

APPLICATION FOR A PRODUCT AUTHORISATION FOR

HIGH POTENCY FACTORATE

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ARMOUR PHARMACEUTICAL COMPANY LIMITED, HAMPDEN PARK, EASTBOURNE, EAST SUSSEX, BN22 9AG

NOVEMBER 1981

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APPLICATION FOR A PRODUCT AUTHORISATION FOR

HIGH POTENCY FACTORATE

PART I SUMMARY

1. NAME AND ADDRESS OF APPLICANT

Armour Pharmaceutical Company, Hampden Park, Eastbourne, U.K.

2. NAME AND ADDRESS OF PROPOSED HOLDER OF AUTHORISATION

As in 1. above.

3. NAME AND ADDRESS OF PERSON RESIDENT IN IRELAND

Berk Pharmaceuticals Limited, Dublin Industrial Estate, Glasnevin, Dublin 2.

- 4. ROLE OF PROPOSED HOLDER OF AUTHORISATION
 - (a) As person responsible for composition of the product in Ireland.
 - (b) As person who imports or procures its importation.
- 5. NAME AND ADDRESS OF ACTUAL IMPORTER

Berk Pharmaceuticals Limited, Dublin Industrial Estate, Glasnevin, Dublin 2.

- 6. ACTIVITIES FOR WHICH THE AUTHORISATION IS REQUIRED
 - (a) Selling or supplying the product in Ireland.
 - (b) Importing or procuring the importation of the product.
- 7. PROPRIETARY NAME OF THE PRODUCT

High Potency Factorate

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8. PRODUCT FORM

Vials of lyophilised powder for intravenous injection after reconstitution with Water for Injections B.P.

9. ACTIVE CONSTITUENT

Antihaemophilic Factor (Human).

10. CLINICAL USE

Treatment of Haemophilia A resulting from deficiency of Antihaemophilic Factor (Factor VIII).

11. RECOMMENDED DOSAGE

Dosage should be adjusted according to the patient's individual needs. Generally one unit of Factor VIII activity per kg will increase circulating Factor VIII level by 2%.

The following general doses are suggested:

- (1) Overt bleeding Initially 20 units per kg of bodyweight followed by 10 units per kg every eight hours for the first 24 hours and the same dose every 12 hours for the next 3 or 4 days. For massive wounds give until bleeding stops and maintain with 20 units per kg 8-hourly to achieve a minimum Factor VIII level of 40%.
- (2) Muscle Haemorrhages
 - (a) Minor haemorrhages in extremities or non-vital areas:
 10 units per kg one a day for 2 3 days.
 - (b) Massive haemorrhage in non-vital areas:
 10 units per kg by infusion at 12 hour intervals for
 2 days and then once daily for a further 2 days.
 - (c) Haemorrhage near vital organs (Neck, throat, subperitoneal):
 20 units per kg initially; then 10 units per kg every 8 hours. After 2 days the dose may be reduced by one half.
- (3) Joint Haemorrhages

10 units per kg every 8 hours for a day; then twice daily for 1 or 2 days. If aspiration is carried out, 10 units per kg just prior to aspiration with additional infusions of 10 units per kg 8 hours later and again on the following day.

(4) Surgery

Dosages of 30 - 40 units per kg bodyweight prior to surgery are recommended. After surgery 20 units per kg every 8 hours should be administered. Close laboratory control to maintain the blood level of Factor VIII above 40% of normal for at least 10 days post operatively is suggested.

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(5) Dental Extractions

For simple extractions a pre-operative dose of 20 - 25 units per kg, sufficient to raise the Factor VIII level to 50% should be given, followed by intravenous administration of tranexamic acid. For multiple extractions further doses of Factor VIII may be advisable 24 or 36 hours after the operation.

12. SIDE EFFECTS, CONTRA-INDICATIONS, PRECAUTIONS AND WARNINGS

Warnings

Factor VIII is prepared from human plasma, each donation of which has been found negative for hepatitis B surface antigen (HBsAg) by the radioimmunoassay (RIA) method. In addition each batch, after reconstitution as recommended in this leaflet, has been tested and found negative by the RIA method. However since no completely reliable laboratory test is yet available to detect all potentially infectious plasma donations, the risk of transmitting viral hepatitis is still present.

Side-Effects

Products of this type are known to cause mild chills, nausea or stinging at the infusion point.

Precautions

Factor VIII contains low levels of group A and B isohaemagglutinins. When large volumes are given to patients of blood groups A, B or AB, the possibility of intravascular haemolysis should be considered. Such patients should be monitored by means of haematocrit and direct Coombs test for signs of progressive anaemia.

Contra-Indications

There are no known contra-indications to antihaemophilic fraction.

13. METHOD OF RETAIL SALE OR SUPPLY

To hospitals only.

14. METHOD OF SALES PROMOTION

Via the professions as a prescription item.

15. MANUFACTURE OF DOSAGE FORM

Manufacture of the dosage form will be carried out by Armour Pharmaceutical Company, P.O. Box 511, Kankakee, Illinois 60901, U.S.A. Assembly of the product into final containers will be carried out at Armour Pharmaceutical Company Limited, Hampden Park, Eastbourne. Vials of Water for Injections BP supplied in Home Treatment Packs for reconstitution of the product will be supplied by Phoenix Pharmaceuticals, Phoenix Estate, Caerphilly Road, Cardiff, Wales, CF4 4XG.

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16. QUALITY CONTROL

Quality control in-process and on the finished product will be exercised by Armour Pharmaceutical Company, Kankakee, USA.

The responsibility for release of the product, based on batch analysis data supplied with each batch, will rest on the Quality Control Manager at Armour Pharmaceutical Company Limited, Eastbourne.

17. CONTAINERS

High Potency Factorate is supplied in 50 ml (500 or 1000 iu/vial) or 30 ml (250 iu/vial) Type I glass vials with 20 mm neck finish. The closure is a grey butyl rubber stopper with an aluminium seal and brown non traumatic flip-top cap. Home treatment packs are made available in certain instances and these contain a vial of Water for Injections BP for reconstitution of the product.

18. LABELLING

Texts for product label and package insert are attached.

19. SAMPLE OF PACKAGED PRODUCT

A sample of the finished product is supplied with this documentation.

20. MANUFACTURING AUTHORISATION

High Potency Factorate is manufactured by Armour Pharmaceutical Company Kankakee, in accordance with Establishment Licence 149, issued by the United States Department of Health, Education and Welfare. A copy of this document is attached.

21. OTHER MARKETING AUTHORISATIONS

High Potency Factorate is licensed for sale in the United Kingdom under Product Licence No. 0231/0044 granted in June 1979.

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PRECAUTIONS Factor VIII contains low levels of group A and B isohaemag-glutinias. When large volumes are given to patients of blood groups A, B or AB, the passibility of Intravascult haemolysis should be considered, Such patients should be monitored by means of laamatocrit and direct Coombs test for signs of pro-gressive ensemia.

CONTRA-INDICATIONS There are no known contraindications to antihaemophilic fraction.

HIGH POTENCY FACTORATE is to be stored below 6°C. When stored as directed, it will maintain its labelled potency for the period indicated below 6°C. HIGH POTENCY FACTORATE is supplied in single dose vials, there being two sizes of vial, dependent on the potency range being used.

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Used to correct desictionus in racus variants with the loading the circulator system COMPOSITION ANUEL STANDARDISATION COMPOSITION ANUEL STANDARDISATION activity in common automic of antihaemophilic activity equivalent to the average Factor VIII content of 1 ml

1000 iu : 50 ml vial 500 iu : 50 ml vial 250 iu : 30 ml vial Potency is stated on each vial label.

P.O.M.

LEGAL CATEGORY

- REFERENCES 1. Abildgaard, "Current Concepts in the Management of Hemophila". From "Current Problems in Pediatric Hema-tology" (Ed. okl. Jaffe and Misscher), Grune and Stratton, 1975. 2. Abildgaard et al. "Current Problems of Pediatric Hema-tology" (Ed. okl. Jaffe and Misscher), Grune and Stratton, 1975.

- Manufactured by Armour Pharmaceutical Company, U.S.A. Distributed by
- PL0231/0044

 August 1980.
 PL0231/

 aliquots of 167 samples of Iresh normal plasma, as determined in an international collaborative study.)
 Each vial also contains sulliciont acdium chloride to make the reconstituted foolution approximately isotonic when Water tor injections.

 RECOMMENDED IECOMMENTUTION Reconstituted foolie precuritors.
 RECOMMENDED IECOMMENTUTION Reconstituted to religications B.P. 500 is 1: 30 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Water for injections B.P. 250 is 1: 10 ml Herek B.P. 250 is 1

- not be used. The solution should be used interpenant should nous of reconstitution. ADMINISTRATION Standard aseptic techniques should be used at all times. Intravenous Injection Floatio diposable syringes are recommended with Factor VIII solution. The ground glass surfaces at all-glass syninges tend to the solution from the vial. Attach a filter needle a tatella diposable syringes. Inset filter needle into stopper of Factor VIII vial; inject air and withdfaw the reconstituted solution from the vial. 2. Discard the filter needle and stach suitable intravenous needle. The solution by the vial inject are and infusion equipment used should comply with that described fin section 3 or 4 of Britis Standard 2463 1962, TACTORATE as recommended under Reconstitution.

Dried Human Antihaemophilic Fraction B.P. (Sterile) **HIGH POTENCY** FACTORATE

To the Medical and Phatmaceutical Professions only.



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- A ttach suitable infusion set.
 Attach suitable infusion set.
 If more than one viails to be administered to the same patient
 the infusion set may be transferred to a second viai.
 When infusion of HIGH POTENCY FACTORATE is complete,
 the infusion set may be flushed with sterile isconic saline to
 avoid loss of any of the reconstituted solution.
 After use, discard infusions are, needles and viails together with
 any unused solution.
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- Atter uso, discard infusion sar, needles and visis togather with any unused solution.
 DSAGE
 HIGH POTENCY FACTORATE is for Intravenous administration only. As a general rule one unit of Factor VIII science in though dosage must be adjusted according to the needs of the patient (weight, severity of haemonhage, presence of inhibitors) the following general dosages are suggested.
 Overt Bleeding—inhially 20 units per kg of body weight followed by U units per kg every sight hours for the first 24 days. For massive wounds, give until bleeding stops and maintain with 20 units per kg eB-hourly to achieve a minimum factor VIII level of 40%.
 Muscle Haemornhagos
- 2.
- minimum Factor VIII lovel of 405.
 Muscle Haemorrhages
 (a) Minor haemorrhages in extremilies or non-vital srees: 10 units per kg once a day for 2 or 3 days.
 (b) Massive haemorrhages in non-vital areas: 10 units per kg by initision at 12 hour intervals for 2 days and then once a day for 2 more days.
 (c) Haemorrhages noar vital organs (neck, threat, sub-perioneal): 20 units per kg initially: then 10 units per kg every B hours. After 2 days the dose may be reduced by one-half.
- by one-half. Joint Hamorrheges—10 units per kg every 8 hours for a day then twice daily for 1 or 2 days. If aspiration is carried out, 10 units per kg just prior to aspiration with additional horizons of 10 units per kg 8 hours later and again on the following day. Surgery—Dosages of 30 to 40 units per kg bodyweight prior to surgery are recommended. After surgery 20 units per kg every 8 hours should be administered. Close laboratory

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Cia Oski, Jaffe and Mieschen', Grune and Straton, 1975. Abildgaard et al. "Treasment of Hemophilia with Glycine— Precipitated Factor VIII" R. Engl. J. Med. 1966, 276, 471. Bangham, Bigg et al. "A Biological Standard for Masure-ment of Biodo Cooguision Factor VIII Activity", Bull. Wid. Biggs et al. "Factor VIII Concentrates Made in the United Kingdom and the Treatment of Haemophilia based on Studies made During 1969-1972", Brit. J. Haematol., 1974, 27, 391. Brinkhous et al. "A New High-Potency Glycine-Precipitated Antihemophilic Factor (AH): Concentrator J. Amer. Med. Ass, 1968, 205, 613. Britton, Hamiston and Abildgaard. "Early Treatment of Hemophilic Hemarthroses with Minimal Dose of New Factor VIII Concentrato", J. Pediat., 1974, 85, 246. Dommandy, "Haemophilia A and B." Preschibers J., 1977, 17, 6.

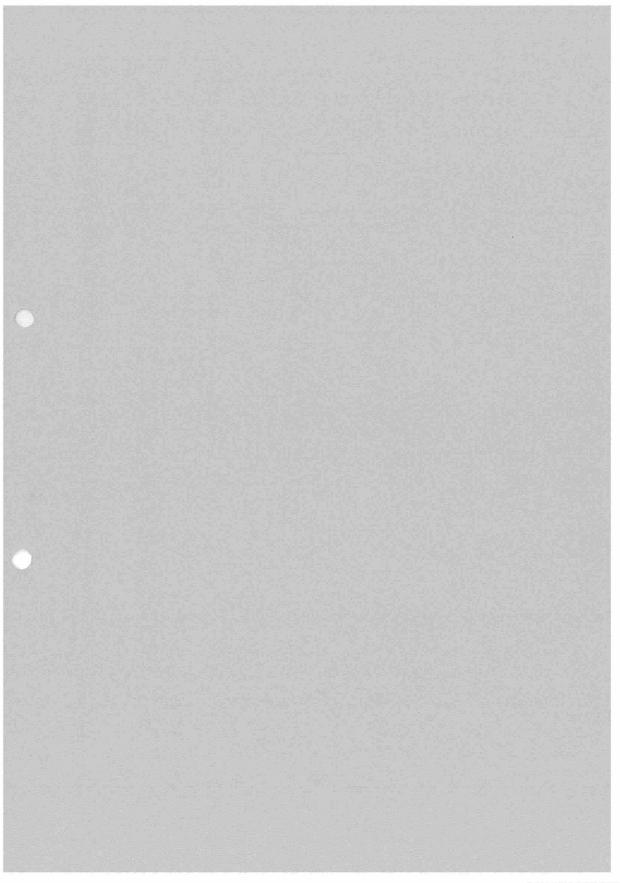
George and Breckenridge. "The use of Factor VIII and Factor IX Concentrates During Surgery". J. Amer. Med. Ass., 1970. 214, 1073.
 Mazza et al. "Antihemophilic Factor VIII in Hemophilia: Use of Concentrates to Permit Major Surgery". J. Amer. Med. Ass., 1970. 211, 1818.
 Nizza 'Clinical Management of Haemophilia'' Br. Med. Bull. 1977. 3, 225-230.

Armour Pharmacoutical Company Limited, Eastbourne, England.

August 1980.

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	DEPARTMENT OF HEALTII, EDUCATION, AND WELFARE WASHINGTON, D.C.
	ESTABLISHMENT DICENSE
	FOR THE MANUFACTURE OF BIOLOGICAL PRODUCTS
	This is to certify that Establishment License No. 149 is hereby issued
	to Armour Pharmaceutical Company, the manufacturer,
	located at Kankakee, Illindis, through the establishment
	identified as Armour Pharmaceutical-Company,
	located at Kankakee, Gilinois,
	pursuant to Section 351 of the Public Health Service Act, approved July 1, 1944 (58 Stat. 702, 42 U.S.C. 262), as amended, and the regulations thereunder. The license authorizes the manufacturer to maintain an establishment for the approximately and the regulations therein the service of th
	for the propagation or manufacture and preparation for sale, barter, or exchange in the District of Columbia, or for sending, carrying, or bringing for sale, barter, or exchange from any State or possession into any other State or possession or into any foreign country, or from any foreign country into any State or possession, any virus, thera-
Ą	product, or arsphenamine or its derivatives, for which the manufacturer holds an unsuspended and unrevoked product license issued by the Secretary of Health, Education, and Welfare pursuant to said Act and regulations.
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	Date_JAN 0 5 1979 GRO-C
	Date_JAN 05 1979



APPLICATION FOR A PRODUCT AUTHORISATION FOR

HIGH POTENCY FACTORATE

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- 1. FINISHED PRODUCT
- 1.1. Description

High Potency Factorate is supplied in 50 or 30 ml Type 1 glass vials containing white to pale yellow lyophilised cake.

1.2. Complete Formula

The formulation of the bulk solution filled into the vials prior to lyophilisation is as follows:

1.2.1. Active

Dried Human Antihaemophilic; .. Approximately 27 iu/ml Fraction BP

1.2.2. Others

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Glycine USP			• •	 		0.2 M
Sodium Citrate USP				 • •		0.04M
Sodium Chloride USP			• •	 	• •	0.04M
Sodium Heparin Injecti	Lon US	SP		 	nmt	1 unit/ml

The lyophilised finished product has the following composition:

Active

Dried Human Ar	ntihaemophilicı		1000,	500 or	250
Fraction BP	1	**		iu/v	ial*

Others

Glycine			 				50	mM/li	itre approx.
					••			nmt	200mM/litre
Citrate	• •		 					nmt	55mM/litre
Heparin	• •	• •	 ••	12		••	$\mathbf{x}_{\mathbf{i}}$	nmt	30 iu/vial

*These potency values are nominal and the actual potency in international units is stated on each vial. Minimal and maximal potencies for these preparations are 80 - 125% of nominal potency in accordance with BP limits.

1.3. Containers

High Potency Factorate is supplied in 50 ml or 30 ml Type 1 clear glass vials with grey butyl rubber lyophilisation stoppers and aluminium seals fitted with brown, non-traumatic flip-top caps.

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2. METHOD OF MANUFACTURE

High Potency Factorate is manufactured from fresh-frozen human plasma which, when tested complies with Raw Material Specification 3029 and has been found negative for Hepatitis B surface antigen activity.

A cryoprecipitate is isolated from thawed human plasma and is dissolved at 25° ± 5°C in glycine-saline buffer containing nmt 3 units/ml Sodium Heparin USP. The pH is adjusted with 0.1N Acetic Acid and/or 0.5N sodium hydroxide and filtered. Impurities are adsorbed onto aluminium hydroxide sterile suspension, centrifuged at approximately 15°C and the preparation stabilised with Sodium Citrate USP and Sodium Chloride USP (both pyrogen-free). The solution is cooled to approximately O^OC and cold ethyl alcohol (95%) added to a concentration of approximately 7%. The precipitate is isolated at low temperature and suspended in citrate-salineglycine buffer. The pH is adjusted to 7.0 \pm 0.2 with 0.5M sodium, hydroxide. This solution may be stored at -40°C or colder if required at this stage. Such frozen solutions are thawed at 34 ± 4°C and brought to final volume with buffer. The pH is adjusted to 5.6 ± 0.3 with 0.5 acetic acid at controlled room temperature (15 - 30°C) and the solution is cooled to 8° C ± 5°C for up to 2 hours. The resulting precipitate is separated and the supernatant clarified by membrane filtration and the pH adjusted to 7.2 ± 0.4 with 0.5 M Sodium Hydroxide.

The solution is membrane filtered and finally sterile filtered through bacterial retentive membrane filters (0.8 μ down to 0.22 μ) before filling into sterile, Type I glass vials. The filled vials are frozen, lyophilised under vacuum and sealed.

A flow chart of the manufacturing procedure is provided overleaf.

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FLOW DIAGRAM (cont.)

PHASE J - Sterile Filtration into Sterile Holding Tanks (Sample submitted for Bulk Sterility Testing)

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PHASE K - Filling (Under Constant Positive Pressure)

PHASE L - Lyophilisation (Under vacuum) and Sealing of Vials for Inspection and Storage at 2-8°C or colder.

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3. QUALITY CONTROL

3.1. Specification of Constituents

Source Plasma (Hum for Antihaemophili								3029
Sodium Citrate USP	••			••	••	$\sim \sqrt{2}$	••	267
Sodium Chloride US	Ρ	e.	••					271
Glycine USP	••	••	••	••	••		••	753
Sodium Heparin Inj	ection	USP	••	••	••		••	2951, 3403, 3404 or 3407
In-Process Materia	ls							5404 OI 5407
Sodium Hydroxide U	SP							USP
Sodium Bicarbonate						••	••	270
Rehsorptar (F-5000 gel - sterile)					••			3232
Glacial Acetic Aci	d USP		••			• •		897

3.2. Analytical Methods

Analytical methods used to define the various criteria cited in the above Specifications are provided in numerical sequence in an appendix to this Section.

3.3. In-Process Control

Physical conditions, ie temperature and pH, used during the manufacturing process are critical and consequently sophisticated telemetry has been developed by the Company to ensure that the required conditions prevail throughout the manufacturing process.

The sterile bulk material is tested for sterility in accordance with the in-house method for bulk sterility testing (Method 303) before filling.

3.4. Finished Product Specification

High Potency Factorate products comply with Finished Product Specification Nos. 31 (1000 iu/vial), 101 (500 iu/ vial) and 102 (250 iu/vial). Copies of these Specifications are attached.

Analytical methods used in determining these specification limits are supplied in the appendix at the end of this Section.

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Specification

Full quality control on the finished product is carried out to the Finished Product Specification by Armour Pharmaceutical Company, Kankakee. Responsibility for release of the product based on the results of the analysis supplied with each batch, rests with the Quality Control Manager, at Armour Pharmaceutical Company Ltd., Eastbourne.

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3.1. RAW MATERIAL SPECIFICATIONS

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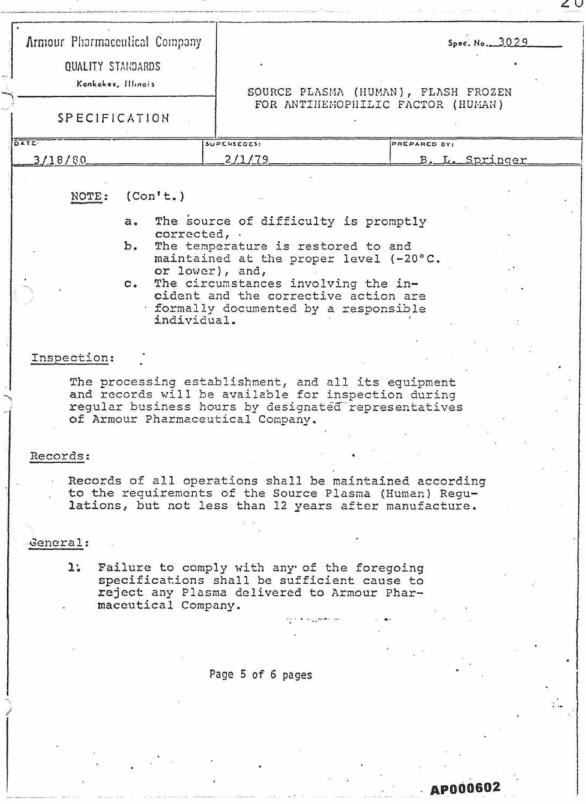
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Armour Pharmaceutical Company		Spec. No. 3029	
QUALITY STANDARDS	•	· /	
SPECIFICATION		UMAN), FLASH FROZEN LIC FACTOR (HUMAN)	
fE: (Sur	PERSEDES:	PREPARED BY:	
	2/1/79		
3/18/80 Description: SOURCE PLASMA (HUMP FACTOR (HUMAN), S-3 blood which has bee by plasmapheresis f hyperimmunized to p intended as source hemophilic Factor (Plasma Protein Frac (Human). It is man all sections of Tit Subchapter F, Parts (640.60 through 640 as individual units after separation fr of withdrawal from contained in the pl by authorized repre Company and the sup Plasma Properties (Speci 1. Substantially f 2. Maximum of 50 m 3. Total Protein c after processin 4. Free of bacteri	2/1/79 AN), FLASH FROZEN, FOR 3029, is the fluid por an stabilized against from adult humans who produce specific antih material for manufact (Human), Immune Serum tion (Human), and Nor nufactured according t the 21 of the Code of a 600, 601, 606, 607, 0.76) of Subchapter F at -70°C. or colder for red blood cells an the donor. The type lasma shall be separat esentatives of Armour oplier.	B. L. Springer R ANTIHEMOPHILIC rtion of human clotting, collected have not been bodies, and ture of Anti- Globulin (Human), rmal Serum Albumin to and conforms to Federal Regulations, 610, and Subpart G and is flash frozen within one hour nd within two hours of anticoagulant tely agreed upon Pharmaceutical Pharmaceutical and 5.5% cells.	
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	- Algeningson - Ageneration - Neutronization (1997) Algoning and Al	AP000598	

	naceutical Company		Spec. No. 3029
	Y STANDARDS		•
	FICATION	SOURCE PLASMA (HUMA FOR ANTIHEMOPHILIC	
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3/10/00		<u> </u>	D. D. Springer
5.	on individual	tis B Surface Antigen as units of plasma by Radio assay meeting requireme 10.40.	immune
6.	Serologically :	non-reactive for Syphill	is.
Labels a	nd Shipping:	т 5.	· ·
1.		xed`to each immediate co l contain all informatio FR 640.70.	
2.		information shall appear to each carton of plasma	
а 1	a. Addressee · Company.	- Armour Pharmaceutical	
	b. Name and fu establishme	all address of blood	
- -	number for "Source Pla	e of and specification material in shipment. asma (Human), Flash Froz mophilic Factor (Human),	en,
1	d. Number and	size of containers in	
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	naceutical Company Y STANDARDS		Spec. No.	3029
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3.	each shipment Company. Reco envelope or ot in one carton be adequately	of the shipment; t marked to facilita	r Pharmaceutical	•
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Armour Pharmaceutical Company QUALITY STANDARDS	-	Spec. No. 3029	
Konkokee, Illinois SPECIFICATION	SOURCE PLASMA (HUMA FOR ANTIHEMOPHILIC	N), FLASH FROZEN FACTOR (HUMAN)	÷
TE [.] Supe	CRSEDCS:	PREPARED BY:	-
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	confirming that all un ash frozen at -70°C.	its ·	
	thin one hour after		
separation fr	rom red blood cells and ours of withdrawal from	đ	
the donor.	burs of withdrawal from	m	
NOTE: Forms simi and B may	ilar to Attachments A		
and D may	NO UDGUI		
Storage Conditional	19 mm		
Storage Conditions:			
The plasma must be ke	ept at temperatures of	-20°C. or lower.	
advertantly ex for 24 hours of equipment fail plasma in stor as Source Plas	er storage temperature ceeds -20°C., but not or less (eg., as a resu ure or power outage), age will continue to o ma (Human), Flash Froz Factor (Human), S-302	-5°C., alt of the qualify zen for	
- continued on ne	ext page -		
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. Р	age 4 of 6 pages		
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Anno						Sp	e. No 30 / 3	
		TY STANCARDS						
	Kon	kakee, Illinois		CE PLASMA (F				
	SPEC	IFICATION	FOR	ANTIHEMOPHI	LIC FA	CTOR (HUMAN)	
	3. 20	TTEATION						
ATE:			SUPERSEDES:		PREF	ARED BY:		
3/1	18/80		2/1/79			B. L.	Springer	Get mer mer fille
c	2.	Armour Pharma right to excl in its opinio problems or u	ude any and n, contribu	d all plasma ute to proce	that ssing	may,		à
	3.	Plasma volume Armour weight gravity.					,	د ^{از} د
0	4.	Plasma bag ta follows:	re weights	used by Arm	our ar	e as		
		b. 800 ml. F c. 2.liter F d. 2 liter M	enwall bag	- 32 gram - 62 gram	S			
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22 ٠ ATTACHMENT A ٠ . DONOR CENTER Plasma Plasma Unit Date of Plasma Carton Unit Date of Carton Plasma Bleeding Volume Number Number Identity Identity Bleeding Volume . ŧ, • * ${\bf \hat{v}}_{i}$ ** . . . · · · · · · ٠ . AP000604

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		N. S.	ACHMENT B	
НОМАМ	PLASMA DATA SHEE	T		14°
(To be submitted with each Armour Pharmaceutical Com	shipment of plas pany, Kankakee, I	ma sent to llinois)	•	
		reason the state of the state o		
Address	•			
	-,			
TYPE OF PLASMA:	. *		×	
Source Plasma (Hu		Shipment	No	
Frozen for Antih Factor (Human)		Quantity	•	Liter
Source Plasma (Hum Frozen for Tetan	us Immune	Date of S	hipment	
Globulin (Human) hemophilic Facto				1
Source Plasma (Hun Source Plasma (Hun				
Tetanus Immune G. Source Plasma (Hur	lobulin (Human)		*	
Source Plasma (Hur	nan) Salvaged			
) for Tetanus Immun (Human)	e Globulin			
This shipment includes plas	sma collected from	a		
from	inclusively, an through	nd sequenti	ally numbe	ered
NTICOAGULANT:	and the same constrained and a		-	
	um Giturta			
Anticoagulant Sodi Anticoagulant Citr Anticoagulant Citr	ate Dextrose	trose		* -
EPATITIS B SURFACE ANTIGEN		×		
Test Used	· · ·			
All units in this shipment non-reactive for Hepatitis	have been tested B Surface Antigen	for and fo	und	
Yes	No			ц.
Bleed numbers of plasma tes fromt dates listed above:	ted and found rea hrough	ctive for (IBSAg use same	
	•			×
Record or dispositon of the	se units are atta	ched.		
An analysis of the second s			AP00060)5

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•					ATTACHMEN	T B (CON'T
ROCE	SSING INFORMATION:	۰.		- ,		
	All units in this shipment colder within one hour afte and within two hours of wit	er separ	ation fr	om red	blood cell	s
	Yes	-			~	
	Explain Exceptions	•	<u></u>			
FORA	GE CONDITIONS:					
	Room Temperature Refrigeration		Freezer Freezer Freezer	(-20°C	0°C.) . or colde: . or colde:	r)
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GNA	TURE		TITLE	-	Marini - Naca Malanza	
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•	Arm	Quality	ceutical Compa Control e, Illinois	ny 		SODIUM	CITRAT	E USP	OR F	Spec. N EAGEI		
		SPECIF	ICATION				• •		*			
	Date:	11/1/73	Supersedes: 5/23/	56	Prepare	d by: G. A.	Portir	iga	Exp. Da	te:	l year	
			PTION: ·			е . Э.					,	
··			ess crysta g, saline t			te, cr	ystalli	ne por	wder.	It	has a	
)		Submit	one 100 co I: RWM bott		bott.	le and	one sh	ell v	ial f	or re	eserve	samp
		TEST	•	÷.		SPECIF:	ICATION		· · ·	2	METHOD	
		Alkalin	fication hity h Drying te			0. K. 0. K. 0. K. 10 - 1: Nil NMt 10 NLT 99	3%	т 100.	. 5%	1	USP USP USP USP USP USP USP	
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All I		100			*	2
QUALITY	accutical Company STANDARDS ee, Illinois	SODIU	M CHLORIDE	.Spec. No.	. 271 EN FREE	
SPECIF	ICATION					
3/9/77		2/14/75		M. S. John	son	
				ic crystals or ste.	*.	
Sampling	:	κ [*]		•	•	
	I - 1 x 120 g ve - 1 x 240 g		- 1 x 5 g.	in sterile bot	tle;	
TEST		SPECIFIC	ATION		METHOD	
Arsenic Barium Heavy me Loss on Iodide o Calcium Sulfate	or alkalinity tals	NaOH Maximum HCl Maximum The solu clear a 2 hours Maximum Naximum No viole yellow Maximum Maximum Nil 99.0 - 1 Satisfac	of 1.0 ml. of 3.12 ml. of 0.0003% tions are ex fter standin of 0.0005% of 0.5% t, orange, of color of 0.005% of 0.015% 01.0% (Dry 1	of 0.02N qually ng for or	U.S.P. U.S.P. U.S.P. U.S.P. U.S.P. U.S.P. U.S.P. U.S.P. U.S.P. U.S.P. U.S.P. U.S.P. U.S.P.	
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Armour Pharmaceutical Company		Spec. No	<u>. 753</u>
QUALITY STANDARDS			
Konkokeo, Illinois	AMINOACETIC ACID,	U.S.P. (GLYC	INE)
SPECIFICATION		٠.	
	ERSEDES	PREPARED BYI	
6/13/79	1/14/77	G. A.	Portinga
Description:	91		15
Aminoacetic Acid occu powder, possessing a to litmus.	rs as a white, odorles sweetish taste. Its s	s, crystalling solution is ac	ne cid
		2	· .
Sampling:	· · •		· .
Group I - 1 x 20 g.; Reserve - 1 x 40 g.	Group X - 1 x 5 g. ste	rile sample;	
TEST	SPECIFICATION		METHOD
Identification Loss on drying Residue on ignition Chloride Sulfate Heavy metals Readily carbonizable	Satisfactory Maximum of 0.2% Maximum of 0.1% Maximum of 0.007% Maximum of 0.0065% Maximum of 0.002%		U.S.P. U.S.P. U.S.P. U.S.P. U.S.P. U.S.P.
Hydrolyzable substances Assay Pyrogen	Colorless solution Satisfactory 98.5 - 101.5% Satisfactory		U.S.P. U.S.P. U.S.P. 208
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Armour Pharmaceu	lical Company	1.5	, .	Sper. No. 3	103
QUALITY STAI Kunkukee, I	10, 17, 540 M	SODTING 1	1111 1 11 1 11 1 11 11 11 11		
SPECIFIC	NOITA		NITS/NL., 10	TION U.S.P., ML. VIAL	
9/30/76	51	5/18/76	brief	G. A. Dunne	
Description			· .	· ·	
A clear a added to derived a not less of the po	sterile solution render the from porcing than 90.0 potency state	ation of sodium solution isoto intestinal me bercent and nor ed on the labe neets U.S.P. re	onic. The sources on the sources of the source of the sources of t	odium heparin xhibits a pote 110.0 percent ed in U.S.P.	is ency
Sampling:		ł			
Group I -	- 3 x 10 ml. - 3 x 10 ml.	vials; Group vials; Reserv	III - 23 x 1 ve - 12 x 10	10 ml. vials; ml. vials.	
TEST	ų. V	SPECIFICATIO	NC	MF	THOD
Sterility Pyrogen pH Assay Volume in co Benzyl alcol	ontainer	Satisfactory Satisfactory 5.0 - 7.5 1000 Units/ Satisfactory 1.0 - 1.5%	y Ml. <u>+</u> 10%	U. U. U. U. U.	S.P. S.P. S.P. S.P. S.P. S.P.
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Armour Pharmaceutical Company QUALITY STANDARDS Kenkekee, Illinois	SODIUM HEPARIN IN	Sper. No. 3404
SPECIFICATION	5,000 UNITS/ML.,	I ML. VIAL
10/28/76	9/30/76	M. S. Johnson
Description:	• .	e e e
added to render the derived from porcin not less than 90.0 of the potency stat	Lution of sodium heparin e solution isotonic. Th he intestinal mucosa. I percent and not more th ted on the label as expr meets U.S.P. requiremen	e sodium heparin is t exhibits a potency an 110.0 percent essed in U.S.P.
Sampling:		
Group I - 25 x l ml Group X - 5 x l ml.	. vials; Group III - 43 vial; Reserve - 56 x 1	x l ml. vials; ml. vials.
TEST	SPECIFICATION	METHOD
Sterility Pyrogen pH Assay Volume in container	Satisfactory Satisfactory 5.0 - 7.5 5000 Units/M1. <u>+</u> 10% Satisfactory	U.S.P. U.S.P. U.S.P. U.S.P.
Benzyl alcohol	1.0 - 1.5% (w/v)	U.S.P. U.S.P.
Benzyl alcohol	1.0 - 1.5% (w/v)	
Benzyl alcohol	1.0 - 1.5% (w/v)	
Benzyl alcohol	1.0 - 1.5% (w/v)	
Benzyl alcohol	1.0 - 1.5% (w/v)	
Benzyl alcohol	1.0 - 1.5% (w/v) Page 1 of 1 page	
Benzyl alcohol	1.0 - 1.5% (w/v)	
Benzyl alcohol	1.0 - 1.5% (w/v)	
Benzyl alcohol	1.0 - 1.5% (w/v)	
Benzyl alcohol	1.0 - 1.5% (w/v)	

Armour Pharmaceutical (
Irmour Pharmaceutical Company QUALITY STANDARDS Konkokee, Illinois		SODIUM	HEPARIN INJ	Spec.	<u>Nu. 3407</u> .Р.,
SPECIFICATIO	И	10,000	UNITS/ML.,	5 ML. VIAI	5
9/30/76	SU F	5/18/76	· · · · · · · · · · · · · · · · · · ·	G. A. DI	inne
Description: A clear ster added to ren derived from not less that of the poten	nder the n porcine nn 90.0 p ncy state	solution iso intestinal percent and n ed on the lab	tonic. The mucosa. It ot more that cl as expre	e sodium hep e exhibits a n 110.0 per essed in U.S	oarin is potency cent S.P.
Heparin Unit <u>Sampling</u> : Group I - 8	ts. It m	neets U.S.P.	requirement	s for injec	tion.
Group X - 1		vial; Reserv	e - 22 x 5		
TEST		SPECIFICAT	·	*	METHOD
Sterility Pyrogen pH Assay Volume in conta Benzyl alcohol	iner	Satisfacto Satisfacto 5.0 - 7.5 10,000 Uni Satisfacto 1.0 - 1.5%	ry ts/Ml. <u>+</u> 10 ry	%	U.S.P. U.S.P. U.S.P. U.S.P. U.S.P. U.S.P.
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Armour Pharmaceutical Company QUALITY STANDARDS Konkeken, Illinois	SODIUM BICARBON/	Spoc. No. 270
SPECIFICATION	00010 <i>m</i> 1710 <i>m</i> .00 <i>m</i>	,
3/7/77	12/15/75	M. S. Johnson
: Description:		
in dry air, but slow when freshly prepare	s a white crystalline p ly decomposes in moist d with cold water, with The alkalinity increas or are heated.	air. Its solutions, nout shaking, are
Sampling:	, ×	
Group I - 1 x 20 g.; Reserve - 1 x 40 g.	Group X - 1 x 2 g. in	ste ri le bottle;
TEST	SPECIFICATION	METHOD
Identification Loss on drying Insoluble substances Normal carbonate	Satisfactory Maximum of 0.25% Complete and clear so Solution does not ass than a faint pink co immediately	sume more
Ammonia Arsenic Heavy metals Assay Pyrogen	No odor of ammonia is Maximum of 0.0003% Maximum of 0.0005% 99.0 - 100.5% Satisfactory	evolved U.S.P. U.S.P. U.S.P. U.S.P. U.S.P. U.S.P. U.S.P.
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Armour Pharmaceutical Company		Spec. N	3232
QUALITY STANDARDS	· .		
Kankakee, Illinois	REHSORPTAR, 1 L	TTER CALIMINIM	NYDROXIDE
SPECIFICATION	STERILE SUSPEN	SION)	hibhohibh,
r E :	SUPERSEDES:	PREPARED BY	
5/6/77	2/20/74	M.S.Joh	nson
× .	*		
Description:			
Rehsorptar, 1 Lite	er (Aluminum Hydroxide,	Sterile Suspen	nsion)
is a sterile, opac	que, white, viscous, th	ixotropic gel.	
Compling	*		
Sampling:	25. a		
Group I - 1 partiz bottles; Reserve -	al bottle; Group III - 1 - 2 x 200 ml. vials.	20 partial fill	l l liter
TEST	SPECIFICATION		HETHOD
Aluminum oxide	1.8 - 2.2%	×.	813
Protein binding capacity	Minimum of 1 mg, pr per mg. Aluminum (854
Specific gravity	0.900 - 1.100	JAIGE	-83B
Sterility	Satisfactory		303
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Armour Pharmaceutical Company QUALITY STANDARDS Konkokee, Illinois		Spec. No 897 IC ACID REAGENT GRADE, U.S.P.
SPECIFICATION		
12/7/76	SUPERSEDES: 7/28/75	M. S. Johnson
Description:	*	· .
Glacial Acetic Aci liquid having a ch	d Reagent Grade, U.S aracteristic pungent	S.P. is a clear colorless t odor.
Sampling:	×	· · · · ·
Group I - 2 x 500 Reserve - No reser	ml. in clean, dry, g ve.	glass stoppered flask.
TEST	SPECIFICATION	METHOD
Assay (Freezing Point Color (APHA) Dilution test Residue after) Not below 16.0°C Not more than 10 To pass test	
evaporation Acetic anhydride Chloride (Cl) Sulfate,(SO ₄) Heavy metals (as Pb) Iron (Fe) Substances reducing	Maximum of 0.001 Maximum of 0.015 Maximum of 1 ppm Maximum of 1 ppm Maximum of 0.5 p Maximum of 0.2 p	A.C.S. A.C.S. A.C.S. A.C.S. A.C.S.
dichromate Substances reducing permanganate	To pass test To pass test	A.C.S.
Suitability for non- aqueous titrations Sensitivity	To pass test To pass test	A.C.S. U.S.P.(Reagent
*U.S.P. specifies A.C	S. test methods.	
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3.4. FINISHED PRODUCT SPECIFICATIONS

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ARMOUR PHARMACEUTICAL COMPANY LIMITED EASTBOURNE ENGLAND

QUALITY CONTROL DEPARTMENT

SPECIFICATION SHEET NO. 31

35

Amended September 1980 (Sheet 1 of 2)

1

HIGH POTENCY FACTORATE (Nominal 1000 i.u./vial) (Dried Human Antihaemophilic Fraction (Sterile) B.P.)

Description:

A white to pale yellow lyophilised cake in a .50 ml vial closed with a brown non-traumatic flip-cap.

Sampling:

Ten pre bulk-shipment vials supplied by Q.C. Department, A.P.C., Kankakee. No samples taken of bulk delivery.

TEST	SPECIFICATION	METHOD
Mammalian Protein	Human positive Bovine and porcine negative	351/K
Potency	Not less than 800 i.u./vial (not less than 26.5 i.u./ml when reconstituted with 30 ml Water for Injections B.P.)	В.Р.
Heparin	Not more than 30 i.u. per vial	1073/K
Total Protein	Not more than 600 mg.per vial (not more than 20 g/litre reconstituted)	993/K
Fibrinogen	Not more than 480 mg per vial (not more than 16 g/litre reconstituted)	1344/K
Aluminium	Not more than 180 µg per vial	995/K
Moisture	Not more than 2% w/w	43-D(K)
Freedom from abnormal toxicity (a) Mouse test (b) Guinea Pig test (Injection n.l.t. 538 i.u./kg of body weight)	Passes Test Passes Test	963/K
Pyrogens (10 i.u./ kg body weight)	Passes Test	208/K
Sterility	Passes Test	303/K
<i>2</i>	· *	
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QUALITY CONTROL DEPARTMENT

36 SPECIFICATION SHEET NO. 31

1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 -		Amended September 1 (Sheet 2 of 2)	980
,	Solution Time	Not more than 30 minutes, typically less than 10 minutes	1343/K
	рН	6.8 - 7.4 (when reconstituted with 30 ml of Water for Injections B.P.)	53/K
*	Isoagglutinins	Not more than 1:256 without pre- dilution and typically less than 1:64 when tested against Anti-A and Anti-B.	386/K
	Sodium	Not more than 200 mM per litre (when reconstituted with 30 ml of Water for Injections B.P.)	1301/K
	Citrate	Not more than 55 mM per litre (when reconstituted with 30 ml of Water for Injections B.P.)	1402/K
	Hepatitis B Antigen s	Negative	379/K or 1410/K

Approved by:

Technical Affairs Manager Regulatory Affairs Manager Research & Development Manager Product Manager Manufacturing Manager Chief Analyst

Quality Control Manager

GRO-C Octoh 24th October 190 GRO-C

Date

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ARMOUR PHARMACEUTICAL COMPANY LIMITED EASTBOURNE ENGLAND

QUALITY CONTROL DEPARTMENT

1

SPECIFICATION SHEET NO. 101

Amended September 1980 (Sheet 1 of 2)

HIGH POTENCY FACTORATE (Nominal 250 i.u./vial)

(Dried Human Antihagmophilic Fraction (Sterile) B.P.)

Description:

A white to pale yellow lyophilised cake in a 30 ml vial closed with abrown non-traumatic flip-cap.

Sampling:

Sec. 1

Ten pre bulk-shipment vials supplied by Q.C. Department, A.P.C., Kankakee. No samples taken of bulk delivery.

	AP000619	/2.	.53
Sterility	Passes Test	303/K	
Pyrogens (10 i.u./kg body weight)	Passes Test	208/K	æ
(Injection n.l.t. 538 i.u./kg of body weight)		, x.	
Freedom from abnormal toxicity (a) Mouse test (b) Guinea Pig test	Passes Test Passes Test	963/K	
Moisture	Not more than 2% w/w	43-D(K)	
Aluminium	Not more than 50 µg per vial	995/K	
Fibrinogen	Not more than 120 mg per vial (not more than 12 g/litre reconstituted)	1344/K	
Total Protein	Not more than 150 mg per vial (not more than 15 g/litre reconstituted)	993/K	
Heparin	Not more than 10 i.u. per vial	1073/K	
Potency	Not less than 200 i.u./vial (not less than 20 i.u. per ml when reconstituted in 10 ml Water for Injections B.P.)	B.P.	
Mammalian Protein	Human positive Bovine and porcine negative	351/K	
TEST	SPECIFICATION	METHOD	

AP000619

QUALITY CONTROL DEPARTMENT

Quality Control Manager

SPECIFICATION SHEET NO. 101

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Amended September 1980 (Page 2 of 2) Solution Time Not more than 30 minutes, typically 1343/K less than 10 minutes 6.8 - 7.4 (when reconstituted 53/K pH with 10 ml of Water for Injections B.P.) 386/K Isoagglutinins Not more than 1:256 without predilution and typically less than 1:64 when tested against Anti-A and Anti-B Not more than 200 mM per litre 1301/K Sodium (when reconstituted with 10 ml of Water for Injections B.P.) Citrate Not more than 55 mM per litre 1402/K (when reconstituted with 10 ml of Water for Injections B.P.) Hepatitis B_Antigen Negative 379/K or 1410/K

Approved by: Octabur 7th 1980 Technical Affairs Manager Regulatory Affairs Manager Research & Development Manager GRO-C Production Manager 24-66 Chief Analyst

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ARMOUR PHARMACEUTICAL COMPANY LIMITED ENGLAND EASTBOURNE

QUALITY CONTROL DEPARTMENT

SPECIFICATION SHEET NO. 102

Amended September 1980 (Sheet 1 of 2)

HIGH POTENCY FACTORATE (Nominal 500 i.u./vial)

(Dried Human Antihaemophilic Fraction (Sterile) B.P.)

Description:

14

A white to pale yellow lyophilised cake in a 50 ml vial closed with abrown non-traumatic flip-cap.

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Sampling:

Ten pre bulk-shipment vials supplied by Q.C. Department, A.P.C., Kankakee. No samples taken of bulk delivery.

	TEST	SPECIFICATION	METHOD	*
÷	Mammalian Protein	Human positive Bovine and porcine negative	351/K	t.
	Potency	Not less than 400 i.u./vial (not less than 20 i.u. per ml when reconstituted in 20 ml Water for Injections B.P.)	B.P.	
	Heparin	Not more than 20 i.u. per vial	1073/K	
,	Total Protein	Not more than 300 mg per vial (not more than 15 g/litre reconstituted)	993/K	
)	Fibrinogen	Not more than 240 mg per vial (not more than 12 g/litre reconstituted)	1344/K	4 8
×	Aluminium	Not more than 100 µg per vial	995/K	
	Moisture	Not more than 2% w/w	43-D(K)	
	Freedom from abnormal toxicity (a) Mouse test (b) Guinea Pig test (Injection n.l.t. 538 i.u./kg of body weight)	Passes Test Passes Test	963/K	
	Pyrogens (10 i.u./ kg body weight)	Passes Test	208/K	
	Sterility	Passes Test	303/K	
	F	AP000621		

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QUALITY CONTROL DEPARTMENT

SPECIFICATION SHEET NO. 102

r.	Amended September 19 (Sheet 2 of 2)	80	
Solution Time	Not more than 30 minutes, typically less than 10 minutes	1343/K	1 1 1
рH	6.8 - 7.4 (when reconstituted with 20 ml of Water for Injections B.P.)	53/K	- K
Isoagglutinins	Not more than 1:256 without pre- dilution and typically less than 1:64 when tested against Anti-A and Anti-B	386/K	* *
Sodium .	Not more than 200 mM per litre (when reconstituted with 20 ml of Water for Injections B.P.)	1301/K	
Citrate	Not more than 55 mM per litre (when reconstituted with 20 ml of Water for Injections B.P.)	1402/K	ی بر ج
Hepatitis B _S Antigen	Negative	379/K or 1410/K	

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Approved by:		Date
Technical Affairs Manager		October 7th 1980
Regulatory Affairs Manager		Qch2-7~1750.
Research & Development Manager	GRO-C	Odrah 84 1980.
Production Manager		23 datar 1990
Chief Analyst		14th October 1980
Quality Control Manager	see.	30 17. Uctober 1980

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ARMOUR000828

4. DEVELOPMENT PHARMACEUTICS

The use of Antihaemophilic Fraction Concentrates in the treatment of classical haemophilia A is well established and Factorate, a product similar to High Potency Factorate, is already Licensed for sale in Eire under Product Authorisation Number PA 10/6/1. The high potency product has been developed as the result of further purification procedures which have resulted in an overall increase in the specific activity of the material, coupled with a reduction in the equivalent levels of protein (notably fibrinogen) and heparin present in the finished product. The end result is a product with greater or similar activity with lower risk of compromise to the circulation through excessive levels of protein.

Batch analysis data for three production batches is attached on the following pages.

AP000623

ARMOUR000829

LOT K852032

2

SPECIFICATION* TEST ASSAY DATA AHF Potency a NLT 30 AHF U/Recon. ml 40.6 U/ml and NLT 900 AHF U/Vial 1218 U/Vial AHF Potency NLT 80% of 0 hour 1119 U/Vial Recon. Stability 3 hrs 91.8% of 0 hr at Cont. Rm. Temp.^a Heparin Assay a 0.4 U/ml NMT 1 U/Recon. ml NMT 30 U/Vial 12 U/Vial Total Protein^a For Calculation 44.3 mg/ml or 1329 mg/Vial Clottable Protein^a 28.9 mg/ml or 867 mg/Vial Specific Activity NLT 0.5 AHF U/mg protein or 0.916 U/mg NMT 2.0 mg protein/AHF U 1.091 mg/U Aluminium a LT 0.0002 mg/Recon. ml LT 0.001 mg/25 ml and LT 0.006 mg/Vial Moisture NMT 2% w/w 0.08% pHa 7.23 Identity Human - Positive Passes Bovine - Negative Porcine - Negative Ovine - Negative Safety a Passes Passes Sterility Passes U.S.P. Passes Pyrogens a Passes U.S.P. Passes (40 AHF U/kg) (.5/0/0) Solution Time^a NMT 30' 26 ' Isoagglutinins^a NMT 1:256 Passes (10 AHF U/ml) Hepatitis B Surface Negative Negative Antigen (HBsAg) a Appearance of Cake White to Nearly White White Particulate Matter Thres. 10 µ 1154/ml Thres. 25 µ 551/ml

NOTE: a - Reconstituted with 30 ml Sterile Water for Injection U.S.P.

AP000624

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LOT K852031

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SPECIFICATION* TEST ASSAY DATA AHF Potency a NLT 30 AHF U/Recon. ml 38.8 U/ml and NLT 900 AHF U/Vial 1164 U/Vial AHF Potency NLT 80% of 0 Hour 1203 U/Vial Recon. Stability 3 hrs 103.4% of 0 hr at Cont. Rm. Temp.ª Heparin Assay a NMT 1 U/Recon. ml 0.4 U/ml NMT 30 U/Vial 12 U/vial Total Protein^a 46.3 mg/ml or 1389 mg/Vial For Calculation Clottable Protein^a 32 mg/ml or 960 mg/Vial Specific Activity NLT 0.5 AHF U/ml protein or 0.838 U/mg NMT 2.0 mg protein/AHF U 1.193 mg/U Aluminium ^a LT 0.0002 mg/Recon. ml LT 0.001 mg/25 ml and LT 0.006 mg/Vial Moisture NMT 2% W/W 0.03% pHa 7.15 Human - Positive Passes Identity Bovine - Negative Porcine - Negative Ovine - Negative Safety a Passes Passes Sterility Passes U.S.P. Passes Pyrogens a Passes U.S.P. Passes (40 AHF U/kg) (.1/.5/.2) Solution Time^a NMT 30' 14' Isoagglutinins a NMT 1:256 Passes (10 AHF U/ml) Hepatitis B Surface Negative Negative Antigen (HBsAg) a Appearance of Cake White to Nearly White White Particulate Matter Thres. 10µ 1010/ml Thres. 25µ 422/ml

NDTE: a - Reconstituted with 30 ml Sterile Water for Injection U.S.P.

AP000625

ARMOUR000831

BATCH ANALYSIS RESULTS

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LOT K852030

TEST	SPECIFICATION*	ASSAY DATA
AHF Potency a	NLT 30 AHF U/Recon. ml and NLT 900 AHF U/Vial	43.8 U/ml 1314 U/Vial
AHF Potency Recon. Stability 3 hrs at Cont. Rm. Temp. ^a	NLT 80% of O Hour	1278 U/vial 97.3% of 0 hr
Heparin Assay ^a	NMT 1U/Recon. ml NMT 30 U/Vial	0.4 U/ml 12 U/Vial
Total Protein ^a	For Calculation	45.4 mg/ml or 1362 mg/Vial
Clottable Protein ^a		39.5 mg/ml or 1185 mg/Vial
Specific Activity	NLT 0.5 AHF U/mg protein or NMT 2.0 mg protein/AHF U	0.965 U/mg 1.036 mg/Vial
Aluminium ^a	LT 0.0002 mg/Recon. ml and LT 0.006 mg/Vial	LT 0.001 mg/25 ml
Moisture	NMT 2% w/w	0.04%
рН ^а		7.07
Identity	Human - Positive Bovine - Negative Porcine - Negative Ovine - Negative	Passes
Safety ^a	Passes	Passes
Sterility	Passes U.S.P.	Passes .
Pyrogens ^a (40 AHF U/kg)	Passes U.S.P.	Passes [.2/1.1/.6/.3/.5/.4/.4/.1]
Solution Time ^a	NMT 30'	14'
Isoagglutinins ^a (10 AHF U/ml)	NMT 1:256	Passes
Hepatitis B Surface Antigen (HBsAg) ^a	Negative	Negative '
Appearance of Cake	White to Nearly White	White
Particulate Matter		Thres. 10µ 1106/ml Thres. 25µ 418/ml

NOTE: a - Reconstituted with 30 ml Sterile Water for Injection U.S.P. AP000626

ARMOUR000832

5. STABILITY

The proposed shelf-life is two years when stored at refrigerated temperature (less than 8° C), protected from light. The product may be stored for a period of up to six months at room temperature (less than 25° C) within the shelf-life of the product.

AP000627

ARMOUR000833

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EASTBOURNE	ENGLAND	Document	, ¹
Product:	1	STABILITY REPO	rt 46
HIGH POTENCY FACTORATE (GENERATION IIB)		Number 2	Date January 1981
* *	*		rt No. 1 dated

BATCHES EXAMINED

Batch No.		*						_	Date d	of Mar	nufacture
S 29212	••		٠.	•••	•••	۰.	••			ϕ	1978
T_31803	••						••	<i></i>	••	$\mathbf{\Theta}$	1979
T 34603		• • •		• •							1979

COMMENTS ON BATCHES

The three batches under examination are all commercial production lots. The batches are all of the 1000 iu/vial presentation but in view of the fact that the 500 iu/vial and 250 iu/vial presentations are smaller fills of the same material in the same type of container and closure system, the data given in this report are deemed applicable to the lower strength presentations.

CONDITIONS OF STORAGE

Samples of each batch have been stored at temperatures of $2-8^{\circ}C$ and $15-30^{\circ}C$ (Controlled Room Temperature) and $37^{\circ}C$ for the storage periods 'indicated in the 'Results' section.

CONTAINERS

All batches were stored in the container foreseen for marketing, ie 50 ml Type 1 glass vials fitted with Tompkins 20 mm butyl rubber lyophilisation stopper and one piece aluminium seal.

RESULTS

The results are shown in the tables overleaf. Batches were tested against Armour Pharmaceutical Company, Kankakee Specification equivalent to the Armour Pharmaceutical Company Limited, Eastbourne Specification No. 31.

AP000628

ARMOUR PHARMACEUTICAL COMPANY LIMITED EASTBOURNE ENGLAND	
Product:	STABILITY REPORT 47
HIGH POTENCY FACTORATE (GENERATION IIB)	Number Date 2 January 1981
	Replaces Report No. 1 dated August 1980

(i) Potency

C) ВАТСН	TEMPERATURE OF STORAGE °C	TESTING INTERVAL	POTENCY IN UNITS/VIAL						
	NO.			INITIAL	3 MONTHS	6 MONTHS	12 MONTHS	18 MONTHS	24 MONTHS	
	S29212	2-8	A	1112	975	960	1038	970	920	
		15-30	A.	1113	915	945	1147	965	915	
	T31803	2-8	A	1083	1005	1095	1410	1010	950	
		15-30	A	1083	1035	1185	1230	910	975	
C	T34603	2-8	А	933	945	930	960	915	895	
		15-30	A	933	961	853	1020	945	875	

A = Assay of vial contents

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Analytical Method

The methodology used to determine the potency of the vial is Armour Pharmaceutical Company, Kankakee, Method No. 365.

AP000629

ARMOUR000835

ARMOUR PHARMACEUTICAL COMPANY LIMITED EASTBOURNE ENGLAND	Pharmaceuti Document	cal	3
Product:	STABILITY RI	EPORT	48
HIGH POTENCY FACTORATE (GENERATION IIB)	Number 2	January 1981	
	neuracea	eport No. 1 dated ugust 1980	

(ii) Solution Time

 \bigcirc

	TEMPERATURE	S	OLUTION T	IME IN MI	NUTES/VIA	L
BATCH NO.	OF STORAGE	INITIAL	3 MONTHS	6 MONTHS	12 MONTHS	18 MONTHS
S 29212	2-8 15-30 37	3 - -	7,10 10,13 15,18	9 12	10, 7 10, 6	5,7 5,3
T 31803	2-8 15-30 37	7 7 7	8 8,7 10	10, 8 6, 7	9 5	5 3, 3
T 34603	2-8 15-30 37	9,9, 10 9,9, 10 9,9, 10	9,9 11,10 13,8	15, 8 11	5	2, 2 4, 3

Analytical Method

The methodology used to determine solution time for the vials is Armour Pharmaceutical Company, Kankakee Method 1343.

AP000630

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ARMOUR PHARMACEUTICAL COMPANY LIMITED EASTBOURNE ENGLAND	Pharmaceutic Document	cal	4
Product:	STABILITY RE	EPORT	49
HIGH POTENCY FACTORATE (GENERATION IIB)	Number 2	Date January 19	981
-	Konlacos	eport No. 1 dated ugust 1980	ł

(iii) Moisture

	TEMPERATURE	PE	RCENTAGE MOIS	TURE
BATCH NO.	OF STORAGE °C	INITIAL	6 MONTHS	19 MONTHS
S 29212	2-8	0.28	0.15	
T 31803	2-8	0.0	0.42	0.05
T 34503	2-8	0.24	0.31	

Analytical Method

The moisture content of the lyophilised vial content was determined using Armour Pharmaceutical Company, Kankakee Method 43D.

DISCUSSION OF RESULTS

No undue or unusual effects have been noted in the stability programme and the samples tested met the appropriate specification requirements.

CONCLUSIONS

Based on the stability results obtained with the preparation and with reference to the proven stability of Factorate (see separate report) the product is sufficiently stable to be distributed in the packs listed below and with instructions regarding storage and shelf-life as specified below:

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ARMOUR PHARMACEUTICAL COMPANY LIMITED	Pharmaceutical 5
EASTBOURNE ENGLAND	Document 5
Product:	STABILITY REPORT 50
HIGH POTENCY FACTORATE	Number Date
(GENERATION IIB)	Pr. 2 January 1981
	Replaces Report No. 1 dated August 1980

Packs: Type 1 glass container fitted with butyl rubber lyophilisation stopper and one piece aluminium seal.

SPECIAL INSTRUCTIONS ON THE PACKAGING MATERIAL

Storage:

High Potency Factorate should be stored at a temperature below $8^{\rm O}{\rm C}$ and protected from light. The solution should be used within three hours of reconstitution.

Reconstitution:

Reconstitute High Potency Factorate using the appropriate quantity of Water for Injections B_*P_* as shown below using standard aseptic precautions

1000 iu : 30 ml Water for Injections B.P. 500 iu : 20 ml Water for Injections B.P. 250 iu : 10 ml Water for Injections B.P.

Warm to 20° C - 30° C before reconstitution with the Water for Injections . B.P. Gentle mixing should be employed to avoid frothing.

Validity:

24 months when stored at a temperature below 8°C protected from light.

AP000632

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ARMOUR000838

FLOW DIAGRAM

Manufactu	uring Process for Antihaemophilic Factor (Human), (High Potency)
PHASE A - Coll	lection and Storage of Human Plasma
PHASE B - Iso]	ation of Cryoprecipitate
a) b)	Thewing at $D^{\circ}C \pm 2^{\circ}C$ Centrifugation at $1^{\circ}C \pm 2^{\circ}C \longrightarrow Cryo-Poor Plasma Supernatant$
PHASE C - Diss Lepa	olution of Cryoprecipitate in Glycine-Saline Buffer Containing rin
ь)	pH adjustment Centrifugation/Filtration>Precipitate discarded pH adjustment
	inium Hydroxide Adsorption (Sterile 2% Suspension Added)
	Storing at 15 ⁰ C <u>+</u> 5 ⁰ C Centrifugation and Filtration> Precipitate discarded
PHASE E - Stab	ilisation and Alcohol Precipitation
a) b)	Sodium Citrate, Sodium Chloride additions Addition of Ethanol at 0°C <u>+</u> 2°C
PHASE F - Isol at O	ation of Precipitate by Centrifugation> Discarded Supernatant C + 3°C
PHASE G - Resu	spension of Precipitate in Citrate-Saline-Glycine Buffer
a) j	DH adjusted 7.0 <u>+</u> 0.2 (below −40 ⁰ C)
PHASE H - pH ac filte	justment followed by cooling and filtration through membrane er.
c) t b) (oH adjustment to 5.6 ± 0.3 (at $15-30^{\circ}$ C) Cool solution to $8^{\circ}C \pm 5^{\circ}C $ Precipitate discarded oH clarified solution adjusted to 7.2 ± 0.4 with 0.5 M Sodium Hydroxide
PHASE I - Clari	fication through a Membrane Filtration Assembly
	(see next page)

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6. CONTAINERS

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High Potency Factorate is supplied in 50 ml or 30 ml Type I clear glass vials with 20 mm neck finish. The closure is a grey butyl rubber lyophilisation stopper fitted with an aluminium seal and brown plastic, non-traumatic flip-top cap.

AP000633

ARMOUR000840

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APPENDIX 1 - NUMERICAL INDEX OF ANALYTICAL METHODS

METHOD NO. PAGE NO. 43D Loss of Weight on Drying .. 53 * 1 Determination of pH ... 53K • • .. 55 . . 83K Specific Gravity 57 208K Pyrogen Test (U.S.P.) 59 Supplement 38. Pyrogen Testing of Antihaemophilic Factor (human) Generation IIB, Lyophilised. .. 62 TR 11 AN AN AN AN Supplement 41. Antihaemophilic Factor (Human) Generation IIB (500 iu/vial). .. 63 . . Supplement 42. Antihaemophilic Factor (Human) Generation IIB (250 iu/vial). .. 64 . . 30 3K Sterility Testing - Final Product 65 351K Mammalian Protein Species Identification .. 71 (Agar Diffusion) Determination of Isoagglutinin Titres in 386K Antihaemophilic Factor (Human) 75 . . 963K General Safety Test 79 993K Biuret Assay for Total Protein Content .. 81 . . 995K Atomic Absorption Analysis of Aluminium in Antihaemophilic Factor 84 . . 1073K Determination of Heaprin Content of Cryoprecipitated AHF 89 . . 1257 Solution Time for Generation II Antihaemophilic Factor 91 1.1 1301 Sodium and Potassium Determination .. 93 Supplement 2. AHF Samples with Varied .. 108 Reconstitution Volumes 1344 Determination of Fibrinogen .. 109 . . 1402 Total Citrates in Antihaemophilic Factor 112 1410 Riasure II Antibody to Hepatitis B Surface .. 118 Antigen AP000634

ARMOUR000841

	QUALIT	Y STANDARDS		,		5
	Konk	akee, Illinois	LOSS	OF WEIGHT ON	DRYING	
	ANALYT	ICAL METHOD				
ATL.			SUPERSEDES:		PREPARED DY:	
	9/26/79)	New		<u>λ. Κ. Roop</u>	
	TEST SU	IMMARY				
	vol	latiles for a	'specified lo loss in weig	ength of time. Tht is calcula	suited for removin The sample is re- ted as percent of	
).		* 4			- 1	
	COMMENT					
	a.				care when handling or sulfuric acid.	
	b.	with an act	ive desiccant formed rapidl	. After dryi	should be charged ng, all weighings moisture adsorptio	n
			×	a second	*	
	MATERIA	LS FOR TESTI	NG			
	Α.	Apparatus				
}		or sulf 2. Vacuum	uric acid.		osphorus pentoxide	
	в.	Chemicals				
		1. Phospho: 2. Sulfurio	rus Pentoxide c Acid:			
		чт. Т	8 cap			
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		54
	Pharmaceutical Company VALITY STANDARDS	APC METHOD No. 43D
** 	Konkokee, Illinois	LOSS OF WEIGHT ON DRYING
ANA	LYTICAL METHOD	
TES	T PROCEDURE	
	A. Preparation of	f Moisture Pans or Weighing Bottles
L.	them for 30 m. ployed in the	oisture pans or weighing bottles by placing inutes under the same conditions to be em- determination. After 30 minutes, accurately tainer. This is the tare or empty weight.
r i	B. Procedure	. •
	0.5-1.0 g. of tainer and acc or container p exposed surfac	mple to a fine powder. Uniformly distribute the sample material in the moisture con- curately weigh to determine the gross weight plus undried sample weight. If possible, the ce area of the powdered sample should not be square centimeters.
	phorus pentox: of 12-24 hours microns* measu lent. Maintai ature). After	tainer in a desiccator containing fresh phos- ide or concentrated sulfuric acid for a period s, under a pressure of not more than 500 ured with a McLeod vacuum gauge, or equiva- in the temperature at 20-25°C. (room temper- r drying, remove the container and weigh This weight is the weight of the container mple.
5		s pressure, a dry ice-acetone trap is ween the desiccator and the pump.
INTE	ERPRETATION OF RESU	JLTS
	(Container + undri undried sample.	ied sample weight) - (tare weight) = Weight of
	(Container + undri = Loss of weight o	ied sample) - (Container + dried sample weight) on drying
	Then: Loss of wei Weight of w	ight on drying x 100 = % of sample wt. lost on drying
REFE	RENCE	4
	Armour Method No.	43D, dated 7/1/76
8/20		
0,20		

rmour Pharmace	eutical Company			APC METHOD NO. 53
QUALITY S	TANDARDS	1 J	*	
Konkokee	, Illinois	DETERMIN	ATION OF P	H
ANALYTICA	L METHOD		4 7	
		SUPERSEDES:		PREPARED BY:
11/11/80		New		A. K. Roop
TEST SUMMA		e is determined	on its so	plution using a pH
meter	fitted with	glass and calo	mel electr	odes. Measurements merwise specified.
COMMENTS	1	×		· · ·
	foty Proces	tione. Conoral	laborator	y precautions prevail.
b. Ge on te	neral Preca	utions: Standa hours. For the f the standardi	rdize the most accu	pH meter at least rate results, the rs and sample solu-
MATERIALS	FOR TESTING			
wi		pable of repeat pH units, and :		ements of pH to to within ± 1
bu va	ffers are pl lues, consul	H=4, $pH=7$, $pH=1$	0. For bu in the U.S	nly used prepared ffers of other pH .P. entitled "Buffer
TEST PROCE	DURE .			
The an instru	alyst is adv ction manual		cular inst	turer's operation rument being used H.
- cont	inued on new	kt page -	•	••• 1
		Page 1 of 2	nagos	
		1,490 1 01 C	Pulles.	
			ч.	
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	Lawy Arrest 1.2 and parameters make a required
Armour Pharmaceutical Company	APC METHOD No. 53
QUALITY STANDARDS	
Konkokee, Illinois	
N-	DETERMINATION OF PH
-ANALYTICAL METHOD	· · ·
	•
TEST PROCEDURE (Con't.)
	graph has been copied from U.S.P. XX and ber procedure for standardizing and measuring ;
Solutions for in pH does not expected pH of between them. Buffer Solution temperature at be measured. The temperature calibration co value identica electrodes and the second Buf then fill the ature as the m of the second pH unit of the deviation is n if they are fa "slope" or "te observed pH va Repeat the sta Solutions for values within without furthe the system is the electrodes portions of the the test mater carbon dioxide Reagents, Indi	the pH meter, select two <u>Buffer</u> <u>Standardization</u> whose difference exceed 4 units and such that the the material under test falls Fill the cell with one of the <u>ons for Standardization</u> at the which the test material is to Set the "temperature" control at e of the solution, and adjust the ntrol to make the observed pH l with that tabulated. Rinse the cell with several portions of <u>fer Solution for Standardization</u> , cell with it, at the same temper- aterial to be measured. The pH buffer solution is within ± 0.07 tabulated value. If a larger oted, examine the electrodes and, ulty, replace them. Adjust the mperature" control to make the lue identical with that tabulated. ndardization until both <u>Buffer</u> <u>Standardization</u> give observed pH 0.02 pH unit of the tabulated value r adjustment of the controls. When functioning satisfactorily, rinse and cell several times with a few e test material, fill the cell with ial, and read the pH value. Use -free water (see <u>Water</u> , in the section, <u>cators, and Solution</u>
	test material in pH determinations.
INTERPRETATION OF RESU	LTS
	d pH of the sample solution and if dilution mple was made, state the degree of dilution,
	* · · · · · · · · · · · · · · · · · · ·
11/5/80	
11/5/80 dw	
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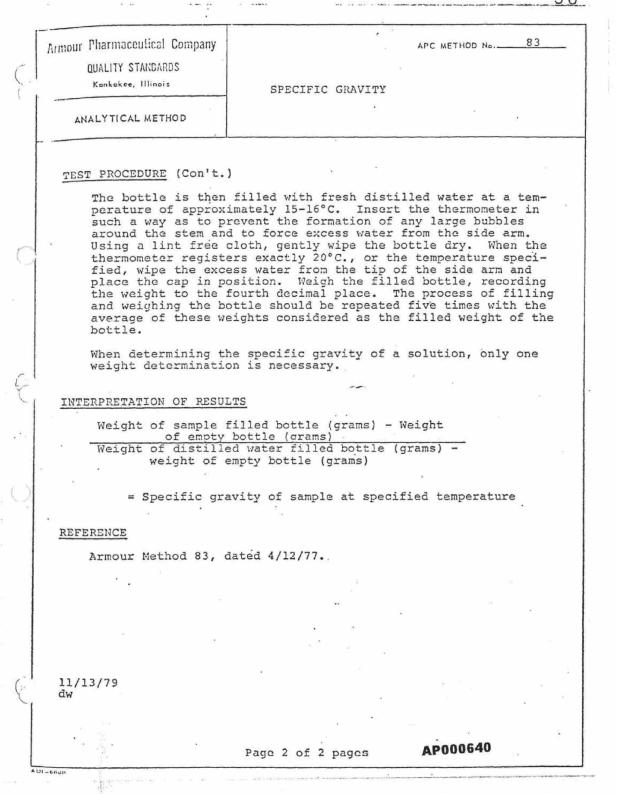
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	Pharmaceutical Co QUALITY STANDARDS	mpany			APO	METHOD NO	83	,
		10 A						
	Kankakee, Illinois		SPECIFIC	GRAVIT	Y			
AN	ALYTICAL METHO	D						
TE:	3/80	SUPERSED			PREPA	RED BY:		
-/		Ner	N			L. Cotter		_
TEST	SUMMARY					A:		ţ
	The specific dividing the by the weight specified ten	weight of the of water of	the subst	ance co	ntained	in a vessel	-	
COM	MENTS							
<u>com</u> ,		2 				_		
	a. <u>Safety Pr</u> condition	s.	Follow	general	labora	tory safety		
130	b. <u>General P</u> arm cap s	recautions: hould be at	The sp psolutely	ecific clean	gravity and dry	bottle and a before use.	side	
MATI	RIALS FOR TES	TING				3		
	1. Specific		tle (Pyc	nometer)			
	 Analytica Distilled Lint free 	water				÷ .		t
	T. MINC LICC	Croth		٠.				
TESI	PROCEDURE		r -			9 (#1		÷
	Calibrate the first weighin place. The a the weight of	g empty wit verage of f	the the the	ermometo hings sl	er and a hould be	side arm cap e considered	in	
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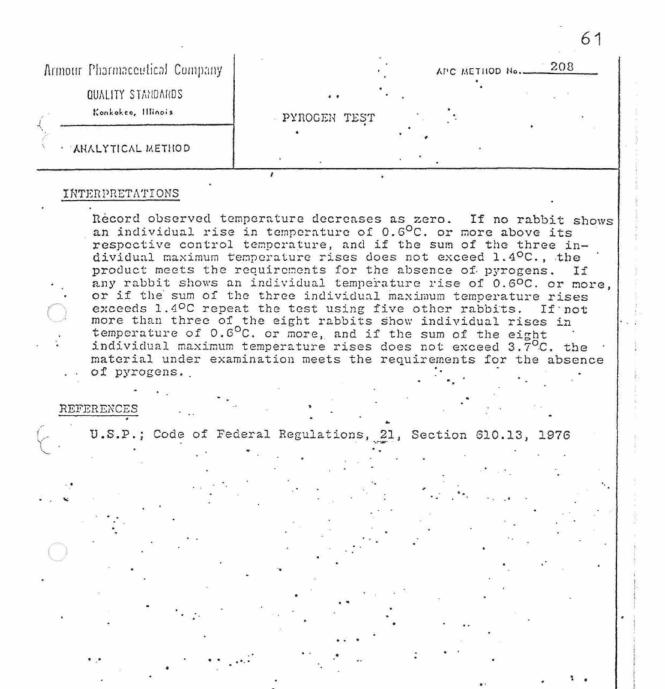
		ALC: A LOCAL DESIGNATION OF THE REAL PROPERTY OF TH	
Armour Pharmaceutical C QUALITY STAIDARDS Konkokoo, Illinois		APC METHO	NO. 208
ANALYTICAL METH	10D .		•
11/23/77	New	PREFARED DYI	otter
TEST SUMMARY	*		
the risks of ministration dose specifi given to the exceed 10 ml	test is designed to li febrile reaction in t , by injection, of the ed for the test is rel patient, but for prac . per kg. of body weig brief period of time.	he patient due to product concerned atcd to that gener tical reasons, it	the ad- . The ally . does not
COMMENTS			
prevail. Ca	utions - General labor re should be exercised cleaning of the equipm	in the handling o	
General Prec	autions - None.		
NATERIALS FOR TE	STING		
 from pyrogen or by any ot 	Render the syringes, n s by heating at 121 ⁰ C. her suitable method. duct to be tested to a	for not less than Just prior to inje	30 minutes
strain that weigh not le in an area o from disturb animal for t	e overtly healthy, mat is commonly used (New ss than 1500 g. House f uniform temperature (ances likely to excite he first time in a pyr at includes all of the	Zealand Whites) ea the animals indiv <u>+</u> 3°C. (<u>+</u> 5° F.)] them. Before usi ogen test, condition	idually and free ng an on it by a
* *	Page 1 of 3 p	ages .	
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Armour	Finantacentical Company	ŀ	· *	/d & me (.60
•	QUALITY STANDARDS Konkokee, Illinois	PYROGEI	N TEST		à
A	NALYTICAL METHOD	· .		•	•
1441	TERIALS FOR TESTING	Con't.			•
	"Test Procedure" of use animals for py 48 hours, nor pric given a test sampl blood products the "Blood Colony" for	rogen tests f r to 2 weeks e that was ac rabbits are	nore frequer following t djudged pyre selected fr	tly than once eve their having been ogenic. For <u>human</u> com the special	ry
0	Temperature Record for which the time known, or any othe sensitivity. Inse of the test animal after a period of as sufficient, rec	r temperature r temperature rt the thermo to a depth o time not less	o reach the e-recording ometer or pr of not less s than that	maximum reading i device of equal obe into the rect than 7.5 cm. and previously determ	s um
•		free normal ion Specifica Water for In	ation No. 32	220	· *
TES	T PROCEDURE	<u>.</u> .			,
Ĵ	Perform the test u under which the an all food from the allowed. If recta inserted throughou with light-fitting a natural resting	imals are hou animals being 1 temperature t the testing neck stocks	used. Durin gused. Acc measuring gperiod, re	ng the test, withh ess to water may probes are to rem estrain the rabbit	old be ain . s
	Not more than 40 m determine the "con base for the deter from the injection only those animals vary by more than animal with a temp	trol temperat mination of a of a test so the control 1°C. from eac	ture" of eac any temperation olution. In temperature th other, an	th animal; this is ture increase resu any one test use as of which do not ad do not use any	the lting
	Unless otherwise s three rabbits 10 m pleting the inject tration. Record t to the injection.	1. of the pro ion within 10	duct per kg) minutes af	ter start of admi	com- nis-
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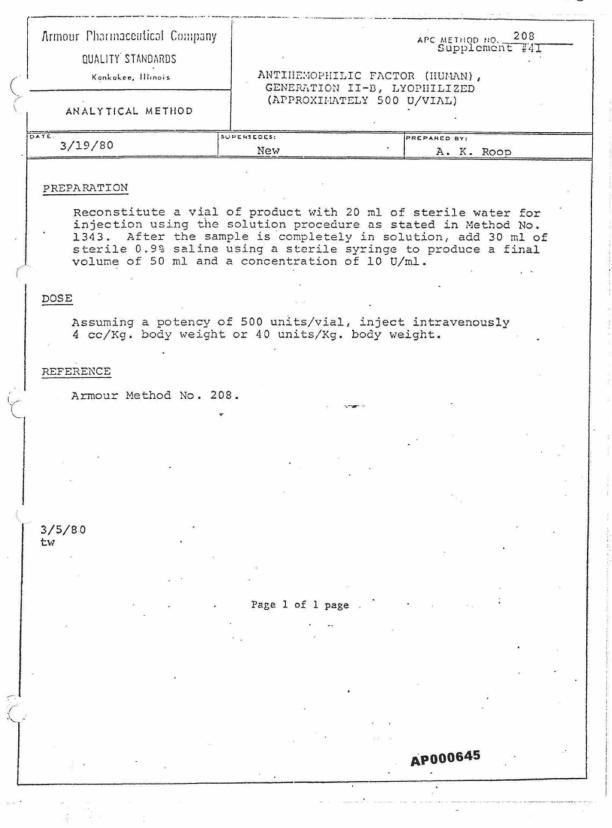
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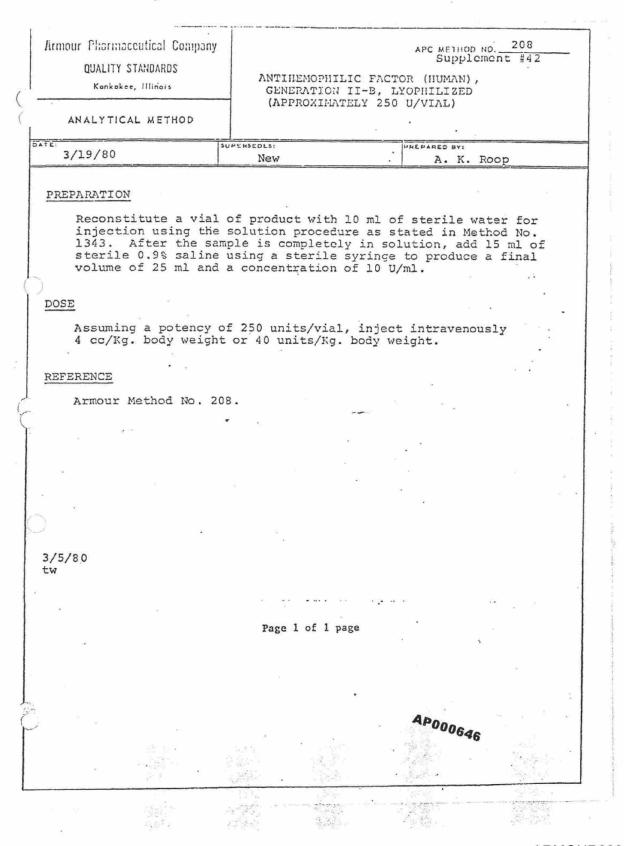
Armour Pharmaceutical Company QUALITY STANDARDS		LITY STANDARDS	APC METHOD NO. 208 Supplement #38			
Konkokee, Illinois ANALYTICAL METHOD			PYROGEN TESTING OF ANTIHEMOPHILIC FACT (HUMAN), GENERATION II-B, LYOPHILIZED			
9/	18/8		4/11/80	A. K. ROOP		
2/			ei e			
1		ARATION	*	,		
) J		for injection usi Method No. 1343.	al of product with 30 ml ng the solution procedur Assuming 1000 U/Vial,* :3.3 with sterile 0.9% s ntaining 10 U/ml.	e as stated in dilute the recon-		
Ī	DOSE	1				
		Inject intravenou weight.	sly 4 ml/Kg body weight	or 40 U/Kg body		
نې د	*If	upon completion of	f the potency assay it i	s discovered:		
		 That the vial is invalid and 	potency is 850 U/V or l d will be performed on t	ess, the test he actual potency.		
- 4 1	a.	excess of the test will be t	pyrogenic and the assay 1000 U/Vial assumed pot invalidated and a new te dose adjusted to 40 U/X	ency, the pyrogen st will be repeated		
Ē	REFE	RENCE	е 			
	. 1	Armour Method No.	208.			
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((Irmour Pharmaceutical Company QUALITY STANDARDS Kenkekse, Illinois	STERILITY TESTING	APC METHOD NO 303
1	ANALYTICAL METHOD	STERILITY TESTING	- FINAL PRODUCT
DAT		SUPERSEDES:	PREPARED BY:
	10/9/80	New	L. Cotter
	TEST SUMMARY		
6	Thioglycollate and less than 14 days	from final containers and Soybean-Casein Digest* After the specified to s found to meed the requ	
1º	COMMENTS	· · · · · · · · · · · · · · · · · · ·	
	a. Safety Precaut	ions: Follow general la	aboratory safety rules.
•	b. <u>General Precau</u> <u>ducted in an a</u>	septic area by trained p	esting must be con- personnel.
1.	should NOT be cond vironmental contro	iniques must be employed fucted in areas under aer of tests, such as exposur withe aseptic sterility t	cosol treatment. En-
	stored in the dark be stored in unsea vided they are tes in sealed containe	edia, if not used within , preferably at 2-25°. led containers for more ted weekly for growth pr rs, the media may be use tested for growth promot	Finished media may than 10 days, pro- comotion. If stored d for one year,
\bigcirc	and fungistatic ac If the product is sterile inactivati	false negative results, tivity for each product bacteriostatic or fungis ng agent must be used or established product ino (Method 309).	must be established. tatic, a suitable in the absence of
	- continued on nex	t page -	And the set of the set
	*BBL designation is tr	ypticase soy broth	
		Page 1 of 6 pages	-
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Armour Pharmaceutical Company QUALITY STANDARDS APC METHOD No. ____ 303___

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Kankokee, Illinois

STERILITY TESTING - FINAL PRODUCT

ANALYTICAL METHOD

COMMENTS (Con't.)

Growth Promoting Test of Media

Each lot of medium is tested for sterility and its growthpromoting gualities. Inoculate two sets of the test medium with not more than 100 spores of Bacillus subtilis (ATCC No. 6633). Likewise, inoculate two sets of test medium with the same number of organisms of Candida albicans (ATCC No. 10231). For Fluid Thioglycollate Medium only, test also two additional sets of medium with no more than 100 organisms of Bacteriodes vulgatus (ATCC No. 8482). Additional organisms may be used. Incubate all inoculated sets of Soybean-Casein Digest medium at 20-25°C and those of Fluid Thioglycollate Medium at 30-32°C. The test media are satisfactory if evidence of substantial growth appears within 7 days. These tests may be conducted simultaneously with the use of the test media "provided; the sterility test is considered unsatisfactory if the test medium shows poor or no growth response (Method '410).

Confirm the sterility of every lot of medium used by incubating samples at the temperature and time specified in the method.

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MATERIALS FOR TESTING

Bacillus subtilis (ATCC No. 6633)
 Candida albicans (ATCC No. 10231)
 Bacteriodes vulgatus (ATCC No. 8482)
 Soybean-Casein Digest made according to USP or purchased commercially
 Fluid Thioglycollate Medium made according to USP or purchased commercially
 Media tubes

- tui - th istr

TEST PROCEDURE

Product Sampling

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For products which are sterilized with steam under pressure in the final sealed containers, select 20 or more units from each sterilizer load. These samples must be representative of all layers of the load. For all other products, select a total of 20 or more units representative of each batch, taken at regular intervals throughout each filling operation.

When testing a lyophilized product, reconstitution should be done according to the directions supplied with the product.

Page 2 of 6 pages

AP000648

		AP000649
121-01		Page 3 of 6 pages
	- continued or	n next page -
	fluid mixture.	
) ml of a sterile aqueous vehicle capable of test material homogeneously throughout the
	transfer 100 r	ng from each of the 10 containers to a flask .
		creat each group as follows. Aseptically
	Soloot 20 cont	cainers, assign them to 2 groups of 10 con-
	3. Oils and Ointr	nents
	mi Soybean-Cas	sein Digest Medium, respectively, and mix.
	and transfer t	to 80 ml Fluid Thioglycollate Medium and 80
	being tested,	or the entire contents if less than 300 mg,
		er. After mixing, withdraw a quantity of prresponding to 300 mg from each container
	amount of ste	rile diluent is added aseptically to the
ł	. If the product	t is soluble or dispersible, the suitable
	2. Crystalline an	nd Powdered Solids
	Intogrycollati	e meutum and incubate 14 days at 20-25 C.
		n Digest Medium with another tube of Fluid e Medium and incubate 14 days at 20-25°C.
	If the produc	t contains mercurial preservative, replace the
	Casein Me	urum, use dupircate containers.
	seeding b	eth the Fluid Thioglycollate and Soybean- dium, use duplicate containers.
	Inoculum	Size). If the volume is not sufficient for
		also plant portions from each container ean-Casein Digest Medium (See chart under
	being tes	ted into Fluid Thioglycollate Medium. In
9	d. Plant por	tions of the material from each container
	with a st	erile hypodermic needle.
	sterile p	ipette or with a sterile syringe fitted
		guids or suspensions for culturing with a
J.	fingers.	
		les by breaking off neck with sterile gloved
		itable bactericidal agent.
		the exterior surfaces of vials and ampules
	· ·	
	1. Liguids and S	uspension
	Testing Techniques	·
	TEST PROCEDURE (Con't	•) • .
	ANALYTICAL METHOD	
		STERIETT TESTING - FIRME FRODUCT
	Kankakee, Illinois	STERILITY TESTING - FINAL PRODUCT
	QUALITY STANDARDS	· . 1
M	rmour Pharmaceutical Company	APC METHOD No. 303

۸	rmour Pharmaceutical Comp DUALITY STANDARDS	any	APC	METHOD No 303			
	Kankokoe, Illinois						
-		STERII	LITY TESTING - FIN.	AL PRODUCT			
	ANALYTICAL METHOD			•			
<u> </u>			-				
	TEST PROCEDURE (Co)	n't.)		÷			
	Testing Technique	es (Con't.)		۵. ا			
	3. Oils and O:	intments (Con't.	.)				
NOTE: The choice of dispersing agent incorporated in the aqueous vehicle may differ according to the nature of the ointment or oil. Before use, test the dispersing agent to ascertain that in the concentration used it has no significant antimicrobial effects during the time interval for all transfers. Mix 10 ml of the fluid mixture so obtained with 80 ml of medium, and proceed as directed under Liquids.							
	Inoculum Size			s.			
Л.,	Vary the minimum volume of medium used according to the content of the final container as follows:						
	Biologicals	•					
	CONTAINER CONTENT	MINIMUM VOL. OF PRODUCT	MINIMUM VOL. OF MEDIUM IF PRESERVATIVE	MINIMUM VOL. OF MEDIUM IF NO PRESERVATIVE			
	10 ml or less	1 ml or total		*			
		content if less than		×			
\cap	Dece 10 to 50 -1	1 ml	80 ml	80 ml			
\odot	From 10 to 50 ml More than 50 ml	l0 ml	80-120 ml 250 ml	80 ml 80-250 ml			
•							
	All Other Final	Products	NTNITHUN NOT OF	NUMBER OF			
	CONTAINER CONTENT	MINIMUM VOL. OF PRODUCT	MINIMUM VOL. OF MEDIUM IF PRESERVATIVE	MEDIUM IF NO PRESERVATIVE			
	Less than 10 ml	1 ml or total	* <u>1</u>				
		contents if less than					
	10 to 49 ml	l ml 5 ml	80 ml 80-250 ml	80 ml 80 ml			
	50 ml or more	10 ml	250 ml	80-250 ml			
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Armour	Pharmaceutical	Company
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APC METHOD No. 303

QUALITY STANDARDS

STERILITY TESTING - FINAL PRODUCT

ANALYTICAL METHOD

TEST	PROCEDURE	(Con't.)	

I	n	C	ub	a	t	i	0	n

Incubate the Fluid Thioglycollate at 30-32°C and the Soybean-Casein Digest Medium at 20-25°C for not less than 14 days.

When the material to be tested renders the medium turbid, so that the presence or absence of growth cannot be determined readily by visual examination, transfer between the third and seventh days, suitable portions of this turbid medium to additional tubes of medium.

Incubate both the original and sub-culture tubes for not less than 7 additional days after the transfer and for a total of not more than 14 days.

--- Examine tubes daily and at the end of the incubation period for the presence of growth. All tubes showing growth are verified by microscopic examination of stained smears (Armour Method 310).

-If no growth is found, the material under examination meets the requirments for STERILITY. If evidence of microbial growth is found the material tested fails to meet the requirements of the test for STERILITY, unless it can be demonstrated by retests or by other means that the test was invalid for causes unrelated to the article.

In view of the possibility that microbial growth observed in the test was due to inadequate aseptic sampling and testing technique rather than to intrinsic contamination of the article, the following retests are permitted.

Complete the attached form and file with Quality Assurance - Product Control (S.O.P. C-28).

First Retest

A UI - 00 Ju

The number of specimens selected, the volumes to be tested, and the media are the same as those indicated for the original STERILITY TEST. If no evidence of microbial growth is found, the material tested meets the requirements of the test for STERILITY. If microbial growth appears in this First Retest, isolate and characterize the microbial contaminant(s) of the

- continued on next page -

Page 5 of 6 pages

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1	Irmour Pharmaceutical Company	APC METHOD No 303
	DUALITY STANDARDS	
	Konkokee, Illinois	
(_	Konkokee, Illinois	STERILITY TESTING - FINAL PRODUCT
2		
Ĩ.	ANALYTICAL METHOD	,
-		
	TEST PROCEDURE (Con't.	
	Incubation (Con't.)	
	First Retest (Con'	t.)
6	STERILITY TEST. I readily, the mater of the test for ST	ompare to the contaminant(s) of the original f the contaminant(s) cannot be differentiated ial tested fails to meet the requirements ERILITY. If the contaminant(s) can be dily, a <u>Second Retest</u> may be performed.
	Complete the attac Product Control (S	hed form and file with Quality Assurance
	Second Retest	
5	in the original ST volumes tested from	imens selected is double the number tested ERILITY TEST and in the <u>First Retest</u> . The m each specimen and the media are the same for the original_STERILITY TEST and the
	tested meets the re growth appears in	nicrobial growth is found, the material equirments of the test for STERILITY. If this <u>Second Retest</u> , the material tested fails ements of the test for STERILITY.
L		etation of allowable results for human ets, see 21 CFR 610.12 (a2) (b).
	REFERENCES	
	United States Pharm	nacopeia, XX
	Code of Federal Reg 610.12.	gulations, Title 21, Part 610, Section
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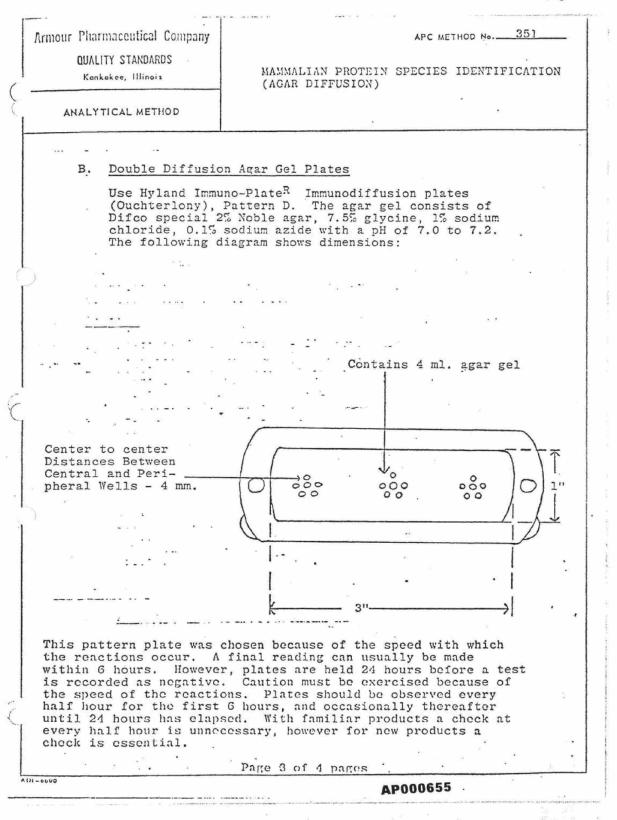
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		Page 1	of 4 page	35		
	an i saara	9° - 1 6.45	• • • •	÷. • •	÷_ *	
	. slower reactio pected reactio					
	procedure. Re 	actions igerator	appear to temperat	o quickly ures (2 to	and are fainter 8 ⁰ C.) cause a	_
	2. Room temperatu					
)	the antiserums	s will us	sually rea	ct with on	e another due b each antiserum.	
в.	General Precaution		· · · ·	, 	·	
	2. Practice gener	· .	ratory sai	ety regula	tions.	
					i en este a compañía de la compañía	
awareness of this practice should be noted when handling human blood derivatives since there exists an inherent 'risk of hepatitis infection.						
	1. Personal hygie					
Α.		5:				-
COM	IMENTS:		· · · · ·	r ann an C	. 1. 11.	
	corresponding anti					
)	method, an antise: fused with a mater	rum conta	aining spe	cific anti	bodies is dif-	
	or absence of human	nn, bovi	ne, ovine	or porcine	proteinaceous	
160	T SUMMARY:	n test i	e used to	domonation	a the processes	
		,	,			
ra Xara	10/12/77	N	ew	in the second	R. H. Brown	
TE:	and the second	SUPERSEDES	:	PR	EPARED BY:	
A	NALYTICAL METHOD			,	• .	
	Konkukee, Illinois		AMMALIAN P AGAR DIFFU		ECIES IDENTIFICATIO	N
	QUALITY STANDARDS	1				

Ar	mour	Pharm	acculical Company			APC	METHOD No	351
	(STANDARDS		ALIAN PROTE R DIFFUSION		ES IDENTI	FICATION
	AN	ALYTIC	CAL METHOD	. .				
	MATI	ERIAL	S FOR TESTING					
	Α.	Anti	serums to be l	sed				
	ن <u>ا</u>	2. 3.	Rabbit Anti-Ov Rabbit Anti-Bo Rabbit Anti-Po Rabbit Anti-Hu	vine Serum rcine Serum	n	•••		•
2		with note prop	antiserums sho other animal d, an antiseru riate protein ugh commercial	proteins. m may be sp (antigen).	Iî any cro pecifically Antiserum	ss-react absorbe	ions are d with ap-	
	в.	Cont	rols				×	÷.
 Positive Ovine Control - 25% human albumin prepared to contain approximately 70 ppm ovine albumin. Positive Bovine Control - 25% human albumin prepared to contain approximately 19 ppm bovine albumin. Positive Porcine Control - 25% human albumin prepared to contain approximately 100 ppm porcine albumin. Negative Control - 25% human albumin previously tested and known to be negative against ovine, bovine and porcine antisera. 				to i to				
	c.	Equi	pment Necessar	y .				
5	.,	2. 3. 4.	Hyland Immuno- Pattern D Capillary pipe Saline Solutio sodium chlori Moist Chamber filter paper.	ttes n - 0.9% sc de in 1000	dium chlor ml distill	ide. Di ed water	ssolve 9 g	ç.
	TEST	PRO	CEDURE		۰.	· · ·		
		Α. 1	Preparation of	Samples fo	r Testing			.*
			 Albumins a and, if ne with salin in 5 ml. s 	re ordinari cessary, ar solution. aline solut	ly tested e diluted (1.25 g. ion).	to this powder	percentage are dissol	ved ·
•.		:	2. Gamma Glob (0.8 g. po	ulins are o wder are di	rdinarily ssolved in	tested a 5 ml. s	s a 16% sc aline solu	olution. ation).
			3. Other bloo the packag		to be prep	ared as	described	on .
	•			Page 2	of 4 pages	•		
1-060	sd 2	17/78	3.	Page 2	or a pages	APOO	DEEA	

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	Armour Method No. 3	51.
		51
REFE	RENCES:	
	antiserum and no cr cept Rabbit Anti-Hu	oss-reactions with other antiserums ex-
	For the test to be ing properly: that	valid, positive controls must be function- is a positive 'reaction with the specific
Ç	disappear by 6 hour	(½ to 1½ hours), but may completely s or more. Positive reactions should be pear and are considered a positive test n disappears.
	If excess antigen c	or antibody exists, the reaction will
	If at the end of 24 is negative.	hours no reaction has appeared the test
RESI	ULTS:	
	5 · ·	e la companya de la c
	6. Examine the pla	te occasionally (for the next 18 hours).
	5. Record positive	e results if they appear within 6 hours.
	reactions, i.e. serum well and	as necessary for 6 hours for precipitin , an opaque zone or "line" between the anti- each antigen well. (Indirect lighting may is examination.)
)	3. Place filled pl room temperatur	lates in moist chamber and incubate at . re.
	2. Antigen is usua center well.	ally placed in outer wells; antiserum in This conserves antiserum.
	 Using capillar predetermined r controls. 	y pipettes, fill wells of agar plates in manner with samples to be tested and also
с.	Set-Up and Assay	•
٨	NALYTICAL METHOD	
	Konkakee, Illinois	(AGAR DIFFUSION)
	QUALITY STANDARDS	MAMMALIAN PROTEIN SPECIES IDENTIFICATION
	r Pharmaceulical Company	APC METHOD No. 351

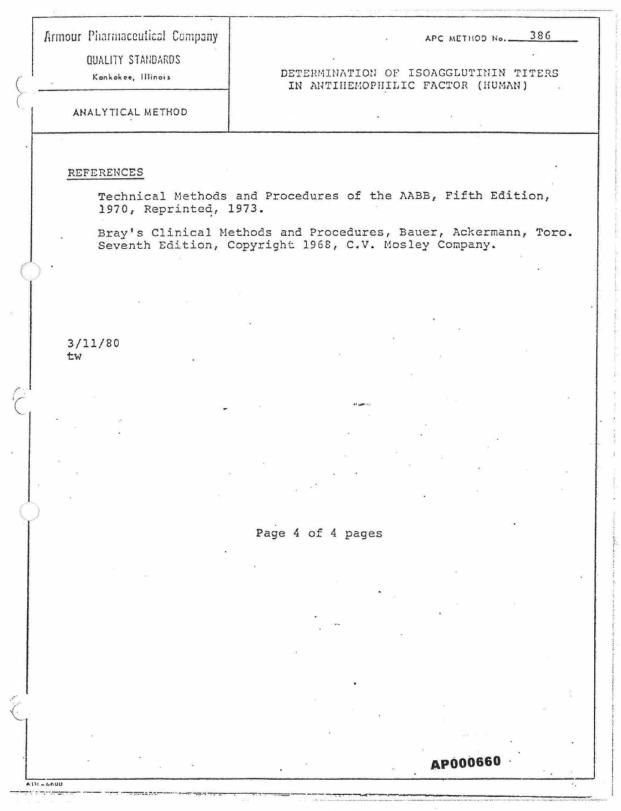
Armour Pharmaceutical Company 386 APC METHOD NO ._ QUALITY STANDARDS DETERMINATION OF ISOAGGLUTININ TITERS Kankakee, Illinois IN ANTIHEMOPHILIC FACTOR (HUMAN) ANALYTICAL METHOD DATE SUPERSCOES: PREPARED BY: New R. Kleszynski 3/14/80 TEST SUMMARY Determine the antiglobulin titer for AHF by incubating washed type A and type B red blood cells with the test material and measuring the degree of cell agglutination which occurs. COMMENTS <u>Safety Precautions</u>: Personal hygiene cannot be overemphasized. Special awareness of this practice should be noted when handling blood derivatives, since there exists an inherent risk of hepatitis infection. MATERIALS FOR TESTING 12 x 75 mm test tubes and racks 1. Physiological saline (9 gms/L.) 2. Adams Sero-fuge 3. Agglutination viewer with light and mirror 4. 5. Coombs serum 6. Eppendorf pipette 0.1 ml and disposable tips 7. 37°C. water bath Fresh anticoagulated whole blood type A and type B 8. Control serum - O serum or plasma with a known A & B titer AHF samples to be tested - <u>Reconstituted According to</u> 9. 10. Label Page 1 of 4 pages

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Armour Phar	maceut	ical Company	. APC METHOD No38.5
QUALITY STANDARDS Konkokee, Illinois			DETERMINATION OF ISOAGGLUTININ TITERS IN ANTIHEMOPHILIC FACTOR (HUMAN)
ANALY	FICAL N	THOD	*
TEST P	ROCED	DURE	
Α.	Pre	eparation o	f Cell Suspensions
			d Type B cell suspension are prepared by resh blood from 3 different A & B donors.
>	2.	a minimum spinning	lood Cells (RBC's) are washed with saline, of three times in an Adams Sero-fuge, one minute at each wash. The supernatant. ded after each wash.
	3.	0.2 ml. o	2% cell suspension in saline by pipetting f each of the washed cell preparations into taining 9.8 mls. of saline. Mix well.
B. Anti-A and An			ti-B 37°C. Saline Titers
	1.		ows of 12 x 75 mm test tubes according to dilutionusually 1:1 through 1:512.
j.	2.	tube in r	first tube in row 1 "sample-A"; the first ow 2 "control-A"; the first tube in row 3 "; and the first tube in row 4 "control-B".
	3.	Use an au into the l in each ro	tomatic pipette to deliver 0.1 ml. of saline bottom of all tubes <u>except</u> the first tube ow.
	4.	1 and 2 or 0.1 ml. or	.1 ml. of sample being tested into tubes f the first and third sample rows. Pipette f the serum control into tubes 1 and 2 of d and fourth control rows.
	5.	in row one	ean pipette, mix the contents of tube 2 (1:2) a several times. Transfer 0.1 ml. to tube (1:4 dilution) in the same row.
	6.	1:32, 1:64 pipette mu	same procedure through dilutions 1:8, 1:16, 4, 1:128, 1:256, and 1:512. A separate 1st be used for each dilution if "carryover" By from one tube to the next is to be avoided.
+	7.	Repeat pro	ocedures 5 and 6 on the next three rows.
í.			
			Page 2 of 4 pages
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ADI-LOUD			AP000658

	acculical Company	APC METHOD No. 386
	Y STANDARDS kee, Illinois	DETERMINATION OF ISOAGGLUTININ TITERS IN ANTIHEMOPHILIC FACTOR (HUMAN)
ANALYTI	CAL METHOD	
TEST PI	ROCEDURE	
В.	blood cel 0.1 ml. c	0.1 ml. of the saline suspension of A red 11s into all tubes in rows 1 and 2; pipette of the saline suspension of B red blood to all tubes in rows 3 and 4. Shake tubes
	9. Incubate	all tubes for 15 minutes at 37°C.
)	10. Centrifug	ge all tubes in Adams Sero-fuge for 45 seconds.
		ed cell button is gently dislodged, observed pically and graded as follows:
	3+ Cell 2+ Cell of r 1+ Cell defi 0 Cell	button remains in one clump button dislodges into several clumps button dislodges into many small clumps nearly equal size button dislodges into finely granular, but inite, small clumps button dislodges with an absence of dis- nible clumps
	1+ agglut	bint is expressed at the dilution of which Lination is seen and reported as the Anti-A -B 37°C. saline titer.
с.	Coombs Antigl	lobulin Titer
		negative and 1+ tubes 3 times with saline, ging 45 seconds after each wash.
	(Coombs)	e third washing, perform an antiglobulin test by adding 2 drops commercial Coombs each tube and centrifuge 45 seconds.
	 Again obs the same PROCEDURE 	erve macroscopically for agglutination using criteria as in Step 11, Section B, of TEST
,	range to	the control serum should be in the expected assure assay results on the product being to correct.
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METHOD NUMBER 963

GENERAL SAFETY TEST

Product To Be Tested:

The general safety test shall be conducted upon a representative sample of the product in the final container from every final filling of each lot of the product. If any product is processed further after filling, such as by freeze-drying, sterilization, or heat treatment, the test shall be conducted upon a sample from each filling of each drying chamber run, sterilization chamber, or heat treatment bath.

Test Animals:

Only overtly healthy guinea pigs weighing less than 400 grams each and mice weighing less than 22 grams each shall be used. The animals shall not have been used previously for any test purpose.

Procedure:

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The duration of the general safety test shall be 7 days for both species, except that a longer period may be established for specific products in accordance with the following paragraph entitled Test Variations. After a specific duration of the test period for a specific product has been established, it cannot be varied subsequently, except in accordance with the paragraph entitled Test Variations. Each test animal shall be weighed and the individual yeights recorded immediately prior to injection and on the last day of the test. Each animal shall be observed every working day. Any animal response including any which is not specific for or expected from the product and whic may indicate a difference in its quality shall be recorded on the day such response is observed. The test product shall be administered as follows:

- Liquid product or freeze-dried product which has been reconstituted as directed on the label. Inject intraperitoneally 0.5 milliliter of the liquid product or the reconstituted product into each of at least two mice; and 5.0 milliliters of the liquid product or the reconstituted product into each of at least two guinea pigs.
- 2. Freeze-dried product for which the volume of reconstitution is not indicated on the label. The route of administration, test dose, and diluent shall be as approved by the Director, Bureau of Biologics, in accordance with the paragraph entitled Test Variations. Administer the test product as approved on at least two mice and at least two guinea pigs.

AP000661

Method Number 963

Non-liquid products other than freeze-dried product. The route of administration, test dose, and diluent shall be as approved by the Directo Bureau of Biologics, in accordance with the paragraph entitled Test Variations. Dissolve or grind and suspend the product in the approved diluent. Administer the test product as approved on at least two mice and at least two guinea pigs.

Test Requirements:

A safety test is satisfactory if all animals meet all of the following requir ments:

1. They survive the test period.

- 1
- They do not exhibit any response which is not specific for or expected from the product and which may indicate a difference in its quality.
- They weigh no less at the end of the test period than at the time of injection.

Repeat Tests:

- 1. First repeat test. If a filling fails to meet the requirements of the <u>Test Requirements</u> in the initial test, a repeat test may be conducted on the species which failed the initial test, as prescribed in <u>Procedure</u> The filling is satisfactory only if each retest animal meets the require ments prescribed in <u>Test Requirements</u>.
- 2. Second repeat test. If a filling fails to meet the requirements of the first repeat test, a second repeat test may be conducted on the species which failed the test; provided that 50 percent of the total number of animals in that species has survived the initial and first repeat tests. The second repeat test shall be conducted as prescribed in the <u>Procedure</u> except that the number of animals shall be twice that used in the first repeat test. The filling is satisfactory only if each second repeat test animal meets the requirements prescribed in paragraph <u>Test Requirements</u>.

Test Variations:

Variations in the general safety test, such as test dose, route of administration, or duration of the test period may be offered as an amendment to the product license and must receive written approval by the Director, Bureau of Biologics, Food and Drug Administration. Approval will be given only if the license amendment provides substantial evidence demonstrating that the proposed test variation will assure sensitivity equal to or greater than the ter prescribed in this method.

Reference: Code of Federal Regulations, Title 21, Paragraph 610.11

AP000662

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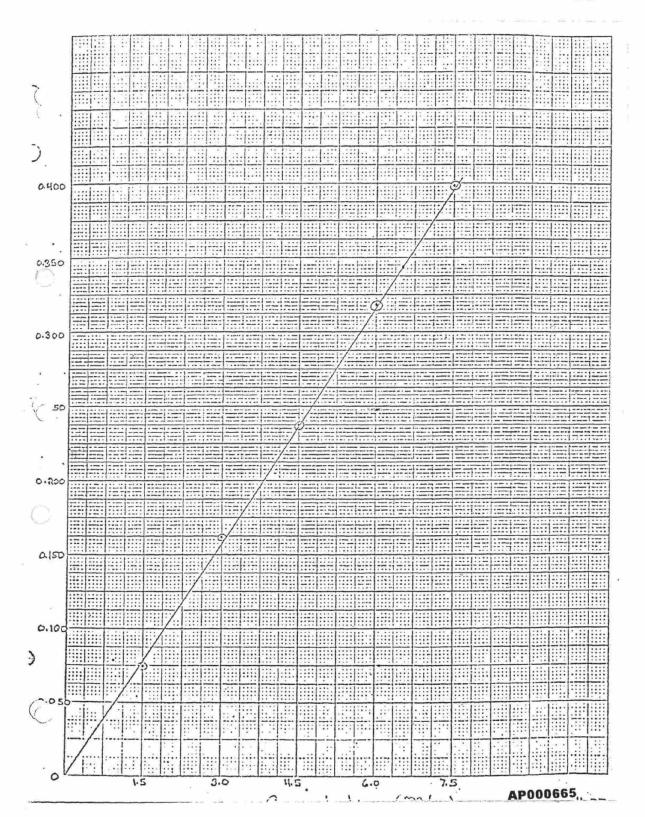
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QUALTY COTTROL DEPARTMENT ANALYTICAL METHODS
(BIURET ASSAY FOR TOTAL PROTEIN CONTENT OF
CRYOPRECIPITATED ANTIHEMOPHILIC GLOBULIN (AHF)
I. Reagents:
 <u>Standard Protein Solution (3 mg./ml.)</u> Dissolve 300 mg. of crystallized human albumin in 75 ml. of dis- tilled water and dilute to 100 ml. with distilled water. The solu tion should be stored at 2 - 8°C. and is stable for 2 months. <u>3 Normal Sodium Hydroxide (NaOH)</u>
Dissolve 120 gms. of sodium hydroxide pellets in 750 ml. of dis- tilled water and dilute to 1 liter with distilled water.
3. <u>6 Normal Sodium Hydroxide (NaOH)</u> Dissolve 240 gms. of sodium hydroxide pellets in 750 ml. of dis- tilled water and dilute to`l liter with distilled water.
4. <u>Biuret Reagent</u> a. Dissolve 17.2 gms. of copper sulfate (anhydrous) in 75 ml. of distilled water and dilute to 100 ml. with distilled water.
 b. Dissolve 173 gms. of sodium citrate dihydrate and 100 gms. of sodium carbonate (anhydrous) in 700 ml. of distilled water. Warm the solution to facilitate solution of the reagents.
c. Cool the two solutions and pour the copper sulfate into the sodium citrate - sodium carbonate mixture.
d. Stir and dilute to 1 liter with distilled water.
e. The Biuret reagent is stable indefinitely at room temperature
I. Preparation of Protein Standard:
 Label a series of 5 test tubes in triplicate as follows: a. l.5 mg./ml.
b. 3 mg./ml. c. 4.5 mg./ml. d. 6 mg./ml. e. 7.5 mg./ml.
 To Λ, add 0.5 ml. of the standard protein solution. To B, add 1.0 ml. of the standard protein solution. AP000663

		·••;
	No. 993	
II.	Preparation of Protein Standard: - continued	
E	To C, add 1.5 ml. of the standard protein solution. To D, add 2.0 ml. of the standard protein solution. To E, add 2.5 ml. of the standard protein solution.	
:	3. To all test tubes add equal amounts of 6 Normal sodium hydroxide.	
5	 To A, B, C, and D, add the required amounts of 3 Normal sodium hydroxide to bring the total volume to 5.0 ml. 	
	Note: E will already be at the required volume of 5.0 ml.	
0	 To all 5 test tubes, add 1.0 ml. of the Biuret reagent and mix well. 	
, î.	 Prepare a blank by mixing 5 ml. of the 3 Normal sodium hydroxide and 1.0 ml. of the Biuret reagent and mix well. 	
	 Use the blank to standardize the spectrometer and determine the optical density of each standard solution at 545 nm. 	
Ċ	 Plot the results on linear graph paper, optical density vs. concost tration. 	
III.	Total Protein of Test Sample:	
	 The amount of sample to be used is estimated so that its value will fall on the standard curve. This is usually done by trial runs. has been found that the following sample size can be used to obtain readings on the standard curve. 	Ī
	 AHF cryoprecipitated sample - If the contents of a vial are reconstituted to 25 ml., the estimated concentration of protes is 15-16 mg/vL Dilute 2.0 ml of this solution to 10 ml. Use 1.0 ml for the assay. 	
	2. To the amount of sample used, add equal amounts of 6 Normal sodium hydroxide. Prepare the test sample in triplicate.	
	3. Dilute to 5 ml. with 3 Normal Sodium Hydroxide.	
•	Add 1.0 ml. of Biuret reagent and mix well.	
12	Prepare blank in same manner as for the standard curve.	
C	. Read at the same wave length as for the standard curve	
	Calculate the amount of protein in the test sample from the standar curve. Correct for sample dilution and express the total protein content in mg./ANF unit.	
-29/77	AP000664	

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Armour Pharmaceutical Company		APC METHOD NO. 095	
QUALITY STANDARDS		,	
Kankakee, Illinois			
ANALYTICAL METHOD		ATOMIC ABSORPTION-ANALYSIS ALUMINUM IN ANTIHEMOPHILIC FACTOR	
OATE:	SUPERSEDES:	PREPARED DY:	
1/28/81	New	Art Roop	
TEST SUMMARY		51	
acetylene flame of a the aluminum in the from an aluminum fil through the flame of ions present in the portional to the com flame. The aluminum comparing the absorp obtained from a seri- tions of aluminum. <u>COMMENTS</u> <u>Safety Precautions -</u> and shut down pro flame can result instrument. Befor manufacturers ope	mple is aspirated into n atomic absorption spe sample is ionized. Ene ament hollow cathode la the instrument is abso flame. The absorption centration of aluminum present in the sample tion of energy due to t es of solutions contain Lack of understanding ocedure of the nitrous in personal injury and ore operation of the in erating instructions an dure for flame ignition	of proper ignition oxide-acetylene damage to the strument, read the definition	
General Precautions -	- None.		
MATERIALS FOR TESTING	<u> </u>		
MATERIALS FOR TESTING	- , Model 303, Atomic-Abs	orption Spectrophotomete thode lamp and a nitrous nit may be used.	
MATERIALS FOR TESTING 1. Perkin-Elmer equipped with oxide burner	- , Model 303, Atomic-Abs h an aluminum hollow ca	thode lamp and a nitrous nit may be used.	
MATERIALS FOR TESTING 1. Perkin-Elmer equipped with oxide burner	- , Model 303, Atomic-Abs h an aluminum hollow ca head. An equivalent u	thode lamp and a nitrous nit may be used.	
MATERIALS FOR TESTING 1. Perkin-Elmer equipped with oxide burner	- , Model 303, Atomic-Abs h an aluminum hollow ca head. An equivalent u Recorder Readout or eq	thode lamp and a nitrous nit may be used.	
MATERIALS FOR TESTING 1. Perkin-Elmer equipped with oxide burner	- , Model 303, Atomic-Abs h an aluminum hollow ca head. An equivalent u Recorder Readout or eq	thode lamp and a nitrous nit may be used.	
MATERIALS FOR TESTING 1. Perkin-Elmer equipped with oxide burner	- , Model 303, Atomic-Abs h an aluminum hollow ca head. An equivalent u Recorder Readout or eq	thode lamp and a nitrous nit may be used.	

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	S 1 A					
An 	mour Pharmaceutical Company QUALITY STANDARDS Konkekee, Minois	APC METHOD No. 995				
	ANALYTICAL METHOD	IN ANTIHEMOPHILIC FACTOR				
	MATERIALS FOR TESTING	(Con't.)				
		ecorder (Houston Instruments) or equivalent.				
	4. Volumetric gl	assware as needed.				
	 Aluminum Standard Solution, 1000 ppm, purchased from Harleco, Item No. 7689 or equivalent. 					
P	6. Sodium Chlori Analytical Re water.	de Solution, 1000 ppm. Dissolve 1 g of agent Grade Sodium Chloride in 1 liter of				
	7. Nitrous oxide	compressed gas.				
1.	8. Acetylene com	pressed gas.				
	9. Necessary control valves and fittings for connecting the compressed gases to the instrument.					
1	REAGENTS					
	Preparation of Sta	andard Aluminum Solutions:				
0	1000 ppm, to a with Sodium Cl Transfer a 10 flasks, respec Chloride Solut	nl aliquot of the Aluminum Standard Solution, a 200 ml volumetric flask, dilute to volume aloride Solution, 1000 ppm, and mix well. and 20 ml aliquot to two 100 ml volumetric stively, and dilute each to volume with Sodium tion, 1000 ppm, to produce two final solutions and 2 ppm aluminum. Mix well.				
	Preparation of Sam	mple Solution:				
	Refer to the determine the	ollowing table of Specification Nos. to volume of Sodium Chloride Solution, 1000 ppm constitute the sample being tested.				
	SPECIFICATION NO	VOLUME FOR RECONSTITUTION				
	3072	25 ml				
	3086	30 25				
2	3502	50				
T	3807 3913	10				
	3914	20 Page 2 of 5 pages				
1	· · · ·	rage 2 or 5 pages				

A	by Perkin- instruction of the Per- using the With the excent all flames man instruction man Always turn f Experience has flame, flasho either ignite be avoided if oxidant. Thi from air to n systems now h T-junction va part number 3 the nitrous on Elmer atomic equipped with over to nitro	APC METHOD No. <u>995</u> ATOMIC ABSORPTION-ANALYSIS ALUMINUM IN ANTIHEMOPHILIC FACTOR DURES wing Flame Ignition Procedures are presented -Elmer. The analyst is advised to read the on manual and the General Information section ckin-Elmer Analytical Methods book <u>before</u> instrument. eption of the nitrous oxide-acetylene flame, ay be ignited directly as described in the nanual for the appropriate instrument. Suel on last and off first. us shown that with the nitrous oxide-acetylene back is most likely to occur when the flame is d or turned off. These flashbacks can generally the flame is turned on or off with air as the s procedure requires a means of rapidly switchin nitrous oxide. Most instrument gas control wave this capability. For those which do not, a live is available as an acessory (Perkin-Elmer 03-0225). The ignition sequence given below for oxide-acetylene flame is usable on all Perkin- absorption spectrophotometers except those a gas control boxes providing automatic switch- us oxide (gas control boxes 040-0301, 057-0134,
	Konkokee, Illinois NALYTICAL METHOD LAME IGNITION PROCED NOTE: The follow by Perkin- instructio of the Per using the With the exce all flames ma instruction m Always turn f Experience ha flame, flashb either ignite be avoided if oxidant. Thi from air to n systems now h T-junction va part number 3 the nitrous o Elmer atomic equipped with over to nitro	IN ANTINEMOPHILIC FACTOR DURES wing Flame Ignition Procedures are presented -Elmer. The analyst is advised to read the on manual and the General Information section ckin-Elmer Analytical Methods book <u>before</u> instrument. eption of the nitrous oxide-acetylene flame, ay be ignited directly as described in the manual for the appropriate instrument. Evel on last and off first. as shown that with the nitrous oxide-acetylene back is most likely to occur when the flame is ad or turned off. These flashbacks can generally the flame is turned on or off with air as the is procedure requires a means of rapidly switching hitrous oxide. Most instrument gas control have this capability. For those which do not, a live is available as an acessory (Perkin-Elmer 103-0225). The ignition sequence given below for oxide-acetylene flame is usable on all Perkin- absorption spectrophotometers except those is gas control boxes providing automatic switch-
	LAME IGNITION PROCES <u>NOTE</u> : The follow by Perkin- instruction of the Per using the With the exce all flames ma instruction m Always turn f Experience ha flame, flashb either ignite be avoided if oxidant. Thi from air to n systems now h T-junction va part number 3 the nitrous o Elmer atomic equipped with over to nitro	wing Flame Ignition Procedures are presented -Elmer. The analyst is advised to read the on manual and the General Information section ckin-Elmer Analytical Methods book <u>before</u> instrument. eption of the nitrous oxide-acetylene flame, ay be ignited directly as described in the nanual for the appropriate instrument. Evel on last and off first. es shown that with the nitrous oxide-acetylene back is most likely to occur when the flame is ad or turned off. These flashbacks can generally the flame is turned on or off with air as the is procedure requires a means of rapidly switchir ditrous oxide. Most instrument gas control have this capability. For those which do not, a live is available as an acessory (Perkin-Elmer 03-0225). The ignition sequence given below for oxide-acetylene flame is usable on all Perkin- absorption spectrophotometers except those a gas control boxes providing automatic switch-
	NOTE: The follow by Perkin- instruction of the Per using the With the excent all flames man instruction m Always turn f Experience has flame, flasho either ignite be avoided if oxidant. Thi from air to n systems now h T-junction va part number 3 the nitrous o Elmer atomic equipped with over to nitro	wing Flame Ignition Procedures are presented -Elmer. The analyst is advised to read the on manual and the General Information section ckin-Elmer Analytical Methods book <u>before</u> instrument. eption of the nitrous oxide-acetylene flame, ay be ignited directly as described in the nanual for the appropriate instrument. Evel on last and off first. es shown that with the nitrous oxide-acetylene back is most likely to occur when the flame is ad or turned off. These flashbacks can generally the flame is turned on or off with air as the is procedure requires a means of rapidly switchir nitrous oxide. Most instrument gas control have this capability. For those which do not, a live is available as an acessory (Perkin-Elmer 03-0225). The ignition sequence given below for oxide-acetylene flame is usable on all Perkin- absorption spectrophotometers except those a gas control boxes providing automatic switch-
	NOTE: The follow by Perkin- instruction of the Per using the With the excent all flames man instruction m Always turn f Experience has flame, flasho either ignite be avoided if oxidant. Thi from air to n systems now h T-junction va part number 3 the nitrous o Elmer atomic equipped with over to nitro	wing Flame Ignition Procedures are presented -Elmer. The analyst is advised to read the on manual and the General Information section ckin-Elmer Analytical Methods book <u>before</u> instrument. eption of the nitrous oxide-acetylene flame, ay be ignited directly as described in the nanual for the appropriate instrument. Evel on last and off first. es shown that with the nitrous oxide-acetylene back is most likely to occur when the flame is ad or turned off. These flashbacks can generally the flame is turned on or off with air as the is procedure requires a means of rapidly switching hitrous oxide. Most instrument gas control have this capability. For those which do not, a live is available as an acessory (Perkin-Elmer 03-0225). The ignition sequence given below for oxide-acetylene flame is usable on all Perkin- absorption spectrophotometers except those a gas control boxes providing automatic switch-
	all flames ma instruction m Always turn f Experience ha flame, flashb either ignite be avoided if oxidant. Thi from air to n systems now h T-junction va part number 3 the nitrous o Elmer atomic equipped with over to nitro	ay be ignited directly as described in the manual for the appropriate instrument. Suel on last and off first. As shown that with the nitrous oxide-acetylene back is most likely to occur when the flame is ad or turned off. These flashbacks can generally the flame is turned on or off with air as the sprocedure requires a means of rapidly switchin ditrous oxide. Most instrument gas control have this capability. For those which do not, a live is available as an acessory (Perkin-Elmer 03-0225). The ignition sequence given below for oxide-acetylene flame is usable on all Perkin- absorption spectrophotometers except those a gas control boxes providing automatic switch-
· · · ·	Experience ha flame, flashb either ignite be avoided if oxidant. Thi from air to n systems now h T-junction va part number 3 the nitrous o Elmer atomic equipped with over to nitro	as shown that with the nitrous oxide-acetylene back is most likely to occur when the flame is ad or turned off. These flashbacks can generally the flame is turned on or off with air as the s procedure requires a means of rapidly switchin itrous oxide. Most instrument gas control have this capability. For those which do not, a live is available as an acessory (Perkin-Elmer 003-0225). The ignition sequence given below for oxide-acetylene flame is usable on all Perkin- absorption spectrophotometers except those a gas control boxes providing automatic switch-
· · ·	flame, flashb either ignite be avoided if oxidant. Thi from air to n systems now h T-junction va part number 3 the nitrous o Elmer atomic equipped with over to nitro	back is most likely to occur when the flame is ad or turned off. These flashbacks can generally the flame is turned on or off with air as the s procedure requires a means of rapidly switchin introus oxide. Most instrument gas control have this capability. For those which do not, a live is available as an accessory (Perkin-Elmer 03-0225). The ignition sequence given below for which accetylene flame is usable on all Perkin- absorption spectrophotometers except those a gas control boxes providing automatic switch-
	057-0345, and automatic swi nitrous oxide ments take pla	057-0262). With gas control boxes providing tchover, it is merely necessary to install the burner head. All secondary acetylene adjust- ace automatically. nitrous oxide burner head.
		he acetylene flow (without igniting the flame) t the flow rate to the appropriate value for the nitrous oxide-acetylene flame. Turn lene flow off.
	the switch	air and nitrous oxide supplies turned on, set hing valve to nitrous oxide and adjust the flow he value specified.
	4. Turn the s	switching valve to the air position.
		acetylene on and ignite the flame (air-). Allow the burner head to warm up for inutes.
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Armour Pharmaceutical Company		APC METHOD No. 995
QUALITY STANDARDS Konkokee, Minois	ATOMIC ABSORPTION-	ANALVELE ALIMENTIK
ANALYTICAL METHOD	IN ANTIHEMOPHILIC	
FLAME IGNITION PROCE	DURES continued	
· · · · · · · · · · · · · · · · · · ·	2	
6. Increase nitrous table.	e the acetylene flow to the oxide-acetylene operation	value specified for in the appropriate
	apid motion, turn the swite	ching valve from air
	oxide flame is now operatin can be adjusted as describ	
followed. T from the nit	ishing the flame, the rever he oxidant switching valve rous oxide to the air posit ow is reduced, then turned	is switched rapidly tion, after which the
TEST PROCEDURE	i e se se presente en entre Se se	
photometer, or e and a nitrous ox values for the s	<pre>lmer Model 303 Atomic Absor quivalent, equipped with ar ide burner head, determine ample and standard solution onsisting of a solution of</pre>	n aluminum lamp the absorption ns versus a
	sted instrument settings for	
Perkin-Elmer, Wavelength - 3 Range - UV	Model 303 Atomic Absorption 09.9 nanometers	n Spectrophotometer
Slit - 4	corded on the lamp	· · · · · · · · · · · · · · · · · · ·
Oxidizer - Nit Fuel Flow - In	rous Oxide - Air - 6.0 itially white ball at 8, li	ght flame, increase
	ow until metal ball is 5.5, r to nitrous oxide. ut	then switch from
Noise Suppre Scale	ssion - 3	· · · · ·
Recorder Setti 0.5 inch/min		· //
· · ·	Page 4 of 5 pages	
54		
AD[0600		AP000669

Armour Pharmaceutical Company

QUALITY STANDARDS

Konkokee, Illinois

ATOMIC ABSORPTION-ANALYSIS ALUMINUM IN ANTIHEMOPHILIC FACTOR

APC METHOD No.

ANALYTICAL METHOD

INTERPRETATION OF RESULTS

Since the absorption values obtained in this analysis are below 10%, there is no need to convert them to absorbance for calculation purposes. Use the absorption of the aluminum standard nearest the sample absorption and calculate the aluminum content of the sample by the following formula:

Sample Absorption x Al std (in ug/ml) = ug Al/ml Standard Absorption

In routine daily use of this procedure, the sample contains less aluminum per ml than the lowest aluminum standard (l ug/ml) as is evident by the visual comparison on the strip chart recorder readout of the sample response to the standard response. To simplify the calculation, the sample response is visually compared to the standard response. The following example is presented to show how the final reported result is obtained. The reconstituted volume is also reported on the Analysis Report sheet.

Example for Spec. No. 3502:

Reconstituted volume = 50 ml. Recorder response less than 1 ppm Al Std. Report - Less than 50 ug Al. per vial Reconstituted volume = 50 ml

If the Recorder response was more than 1 ppm and less than 2 ppm, the report should be:

Less than 100 ug Al. per vial Reconstituted volume = 50 ml

REFERENCE

Perkin-Elmer Operator's Instructions

9/8/80 ml

ALII-DOUD

Page 5 of 5 pages

ARMOUR000877

AP000670

ARMOUR FHARMACEUTICAL COMPANY QUALITY CONTROL DEPARTMENT ANALYTICAL METHODS

METHOD NUMBER 1073

THE HEPARIN CONTENT OF CRYOPRECIPITATED AHF

The following in <u>vitro method</u> is used in the determination of the Heparin cortent of cryoprecipitated AHF. The test is based on the <u>in vitro</u> inhibition by Heparin of coagulation time as measured by the activated partial thromboplastin time procedure.

I. Reagents and Equipment:

- 1. Heparin-potency 1000 units/ml. obtained from a reputable source.
- 2. Activated Partial Thromboplastin
- Cryoprecipitated AHF (Lyophilized)
 (a) Heparin Containing
 - (b) Non-Heparin Containing
- 4. Normal Control Plasma
- A BBL Fibrometer for the determination of clotting times. This instrument should be equipped with an automatic pipette capable of dispensing 0.1 ml.
- 6. 0.025 molar calcium chloride

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7. A Thermal Incubation Block (37°C.).

II. Procedure:

- <u>Reconstitution of Reagents</u>
 1. Reconstitute the normal coagulation control plasma (lyophilized with 1 ml. of 3 (a) or 3(b).
 - 2. Reconstitute the activated partial thromboplastin (lyophilized) with 2 ml. distilled water.
 - Reconstitute the AHF sample (lyophilized) with 25 ml. of distilled water or see appropriate supplement.

- 14 1 AP000671

Method Number 1073

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 Dilution of Heparin for the Preparation of a Heparin Standard
 Dilute the stock Heparin Solution of 1000 u/ml. with distilled water to provide the following concentrations, in 1 ml. of normal coagulation control plasma:

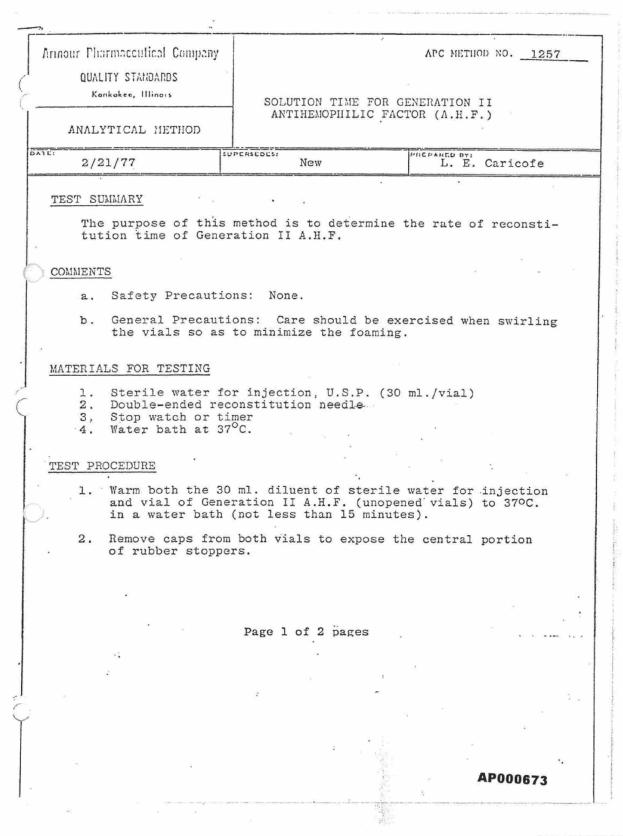
0.25 u/ml., 0.30 u/ml., 0.35 u/ml., and 0.40 u/ml.

- C. <u>Determination of the Clotting Time of the Plasma with Heparin Added</u> 1. Incubate the plasma, partial thromboplastin and 0.025 molar calcium chloride at 37°C. for five (5) minutes.
 - Using an automatic pipette, add 0.1 ml. of the plasma to a
 fibrometer reaction cup.
 - Add 0.1 ml. of partial thromboplastin to the plasma in the reaction cup and incubate exactly four (4) minutes.
 - At the end of four (4) minutes, add 0.1 ml. of calcium chlorid: and start timing of the clotting reaction.
 - 5. Determine the clotting times for these Heparin containing plasma in 5 replicate determinations and plot on standard grap: paper. Plot clotting time on the vertical axis and the Heparin content on the horizontal axis.

D. Determination of the Heparin Concentration in the AHF Sample

- Reconstitute 1.0 ml. of normal coagulation control plasma with 1.0 ml. of the reconstituted AHF sample. Mix and incubate at 37°C. for five (5) minutes in a thermal block.
- Determine the activated partial thromboplastin clotting times in 5 replicate determinations.
- 3. Calculate the Heparin concentrations of the AHF sample from the Heparin Standard and correct for dilution.
- 4. Express the Heparin concentration in units/ml.

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lemotar Pharmace	outical Company		·	APC METHOD NO.	1257
DUALITY S	TANDARDS			¥	t
Konkokee,					
			TIME FOR GEN OPHILIC FACTO		
ANALYTIC/	L METHOD		. ،		
. sto ins rub be	opper of the sert the othe ber stopper drawn into t	diluent vial. r end of the d of the A.H.F.	Invert the louble-ended vial. Allow by vacuum a	e into the rubb diluent vial a needle into th v the diluent t and direct the	nd
- dou fro	ble-ended ne m the A.H.F.	edle; then rem	ove the doub the incomin	nt vial from th ble-ended needl ng airstream to -watch.	e '
wit	hout any agi		permits thor	operature for l rough wetting o postitution.	
to tio	promote break n, more rapid	sup of the cak	e. As more permissable	y (avoid foami cake goes into to get the las	solu-
mus	t be in solut	ion after 30	minutes of c	olution. The ontinual swirl nstitution tim	ing
INTERPRETAT	ION OF RESULT		19		*
Report	the reconstit	ution time to	the nearest	minute.	1
REFERENCES		16 2	×		
Memo to	Mr. A. K. Ro	op from Dr. F	red Feldman	dated January	18, 1977.
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Armou	r Pharmaceutical Company		APC METHOD NO 1301
- 10-0-1-0-1	QUALITY STANDARDS Kankakee, Illinois	Using the Ir	DTASSIUM DETERMINATIONS Instrumentation Laboratory
A	NALYTICAL METHOD	Model 343 FJ	lame Photometer
TE:	2/13/78	supersedes: New	W. H. Osgood
TE	ST SUMMARY	L.	
)	sodium and potass Photometry. The and as a radiatic the variability of concentrations of transfers in the present for prope is applicable onl	sium ions in samples method uses Lithium on buffer. In the la of potassium determin sodium. The variat excited state of the er operation of the i	sing the Instrumentation
СО	MMENTS		· •
	using compres products are transmission	sed gases must be us	
	potassium lev All glassware	els in the range of	must have sodium and the standards described. y clean to avoid vari- n.
3	c. Non-Standard abbreviations		following non-standard
	DD wat	er = distilled deion	ized water
	•		
	с. У	Ŧ	
SON FOR	R REVISION:	A	GRO-C March 28, 1978
	×.,		GRO-C 3/22/2 3/30/18
			GRO-C 4/3/78
	• •		GRO-C 4/6/18
3			ء محمد المحمد ا
be	2/13/78	Page 1 of 11 pages	AP000675

94.

Armour	r Pharmaceutical Company	APC METHOD No
	Kankakee, Illinois US	IUM AND POTASSIUM DETERMINATIONS ing the Instrumentation Laboratory del 343 Flame Photometer
A	NALYTICAL METHOD	
MAT	PERIAL FOR TESTING	· · ·
)	Model #343 2. Compressed air (From minimum, preferred 3. Instrument Grade Pro <u>not</u> substitute. 4. Volumetric Glassware	pratory Digital Flame Photometer n a cylinder or air compressor, 25 p.s. range 30 - 40 p.s.i.) opane. Use IL Cat. #57000 only. Do e (Flasks & Pipets) or medicine cups, approximately_30 ml.
ф.	B. Reagents: Described in	sections where required.
	C. Standards: Described in	a sections where required.
TES'	T PROCEDURE	n ¥
ţ	use Section I only. Section with the approval of the man	For all A.H.F. & N.S.A. samples, A II and III are to be used only ager of the control laboratory. The proper supplement to this
	I. Manual Dilution with II. Manual Dilution with III. Automatic Dilution w IV. Instrument Operation	indirect readout
I.	Manual Dilution with Direct	Results
	prepared using the	hat the standards and samples are same Lithium Internal Standard. olutions are used, the results eaningless.
	A. <u>Reagents</u>	
	Stock concentrate (I well. Substitution	ndard: Dilute 20 ml. of Lithium L Cat. #35003) to one liter. Mix is <u>not</u> recommended since this nonionic surfactant.
		*
	Pa	ge 2 of 11 pages

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1	Discourse	anytical Company	1301
irmour		aceutical Company	APC METHOD No.
		STANDARDS	SODIUM AND POTASSIUM DETERMINATION
	Konkok	ee, Illinois	Using the Instrumentation Laboratory Model 343 Flame Photometer
AA	ALYTIC	CAL METHOD	Notel 545 Flame Photometer
В.	Stan	dards	
	desi		prepared in two ways. The first method is second to be used only when absolutely
۰, "		values. For s 140 meq.Na/l	ndards: Use IL standards of the appropriate sodium analysis of A.H.F. & N.S.A., use and 5 meq. K/liter (Catalog #35140) and and 100 meq K/l (IL Cat. #35100) as the dard.
	1	values of pota values of pota	analysis, use the levels that are close to the assium to be measured. Since the expected assium are less than 5 meq/l, use IL Cat. #35140 tandard (5 meq. K/l) and IL cat. #35120 as the dard.
		standard into of Lithium Int the mark with required which Internal Stand	e standards for use, pipet 1.0 ml. of the a 200 ml. volumetric flask. Pipet 50.0 ml. ternal Standard into the same flask. Dilute to DD water and mix well. A zero-standard is n is prepared by pipeting 50.0 ml. of Lithium dard into a 200 ml. volumetric flask and ne mark with DD water. Mix well.
	-	a. 140 meg Na 14.0 meg o to a 100 m and dilute a 200 ml. Internal S mark with	cds: Use reagent grade (or better) chemicals. A/liter. Weigh out accurately approximately of sodium chloride (819 milligrams). Transfer al. volumetric flask. Dissolve in DD water to the mark. For use, pipet 1.0 ml. into volumetric flask. Pipet 50.0 ml. of Lithium Standard into the same flask. Dilute to the DD water and mix well. If the weight used is calculate the true value of the standard as
		True	e value (meq/l.) =
	ł		5.85
	ł	10.0 meq. to a 100 m	/liter. Weigh out accurately approximately of sodium chloride (585 milligrams). Transfer ol. volumetric flask. Proceed as above (2.a.) with "Dissolve in DD water".
		*	
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		•	Page 3 of 11 pages

ARMOUR000884

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Armou	ir Pha	rmaceutical Company	APC METHOD No. 1301
		ITY STANDARDS	4 · · · · · · · · · · · · · · · · · · ·
		kakee, Illinois	SODIUM AND POTASSIUM DETERMINATIONS
	ANALY	TICAL METHOD	Using the Instrumentation Laboratory Model 343 Flame Photometer
в.	Sta	ndards (Continu	ed.)
	с.	of potassium ch 1000 ml. volume to the mark. F volumetric flas Standard into t DD water and mi calculate the t	Weigh out accurately approximately 5 meq. oride (373 milligrams). Transfer to a cric flask. Dissolve in DD water and dilute or use, pipet 1.0 ml. into a 200 ml. c. Pipet 50.0 ml. of Lithium Internal me same flask. Dilute to the mark with twell. If the weight used is not exact twe value of the standard as below
ž		True	value $(meq/1) = \frac{weight used}{74.6}$
	d.	potassium chlor	Weigh out accurately approximately 2 meq. of de (149.2 mg). Transfer to a 1000 ml volumetri as above (2.c.) starting with "Dissolve
С.	Sam	ple Preparation	* 4
,	1.	For A.H.F. samp	es: Reconstitute the samples as specified in the specification. Use the recon- stituted solution and follow the method below for N.S.A. samples.
	2.	For N.S.A. samp	es: Pipet accurately and precisely 1.0 ml. of the sample into a 200 ml. volumetric flask. Pipet 50.0 ml. of Lithium Interna Standard into the flask. Dilute to the mark with DD water and mix well.
	3.	For all other s assistance.	mples, see the supplement or seek qualified
D.	Metl	hod of Operation	- Refer to Figures 1, 2, 3 & 4.
	1.	in 30 ml. dispo from the top.	be aspirated into the instrument are put able beakers to the same level, 3/16" uring aspiration, the beakers are placed 0 ml. beaker under the aspirating tube.
	2.	Refer to Section	IV for Instrument Operation and turn on.
	з.		up containing DD water under the aspirating t to draw for several seconds.
	4.	Remove this and	wipe the aspirating tube.
		Using the	wing is written for sodium determinations. potassium standards and making corrections ontrols, the procedure is applicable to determinations.
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APC METHOD No	rmour Pharmaceutical Company		
SODIUM AND POTASSIUM DETERMINATIONS Using the Instrumentation Laboratory Model 343 Flame Photometer	TY STANDARDS okee, Illinois		
	ICAL METHOD	ANALYT	
sodium standard under the aspirating tube	Place the zero and allow it t	5.	
tal displays and the meter have settled, set esponse Meter Needle (No. 2 on figure 2) at see figure 4) using the Lithium Set Control are 2).	the Lithium Re	6.	
lium Digital Concentration Display (No. 4 on 000.0 using the Sodium Zero Control (No. 16 Operate the Sodium Decimal Position Button are 2) to place the decimal point at the on (000.0).	figure 2) to 0 on figure 3).	7.	
o Standard Solution and wipe the aspirating ir to draw for about 10 seconds.		8.	
est level of sodium standard under the tube and allow it to draw.		9.	
After the digital displays and the meter have settled, adjust the Sodium Digital concentration display to the value of the standard using the Sodium Balance Control (No. 3 on figure 2). If the standard used is the Cat. #35140, the display would be adjusted to 140.0.			
ndard and allow air to aspirate for approx- nds.	Remove the sta imately 5 seco	11.	
briefly under the aspirating tube (\sim 2 seconds) air to aspirate for approximately 5 seconds.		12.	
ange standard under the aspirating tube and aw.	Place the midrallow it to dr	13.	
lays and meter have settled, record the value m Digital Concentration Display as milli- dium per liter.	from the Sodiu	14.	
ue should be within approximately + 1 meq. of or label) value. If it is not, recheck the tandard and reset if necessary. If this does e problem, prepare new dilutions of the standards ot correct the problem, seek qualified	the prepared (higher level s not correct the	, 51	
Page 5 of 11 pages AP000679			

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Armo	uir Phari	maceutical Company	APC METHOD No
QUALITY STANDARDS Konkokee, Illinois			SODIUM AND POTASSIUM DETERMINATIONS Using the Instrumentation Laboratory Model 343 Flame Photometer
	ANALYI	ICAL METHOD	*
	15.	air to aspirat briefly under	ution from under the aspirating tube and allow e for approximately 5 seconds. Place DD water the aspirating tube (~ 2 seconds) and then spirate for approximately 5 seconds.
	16.	Place the samp draw.	le under the aspirating tube and allow it to
	17.	the value from	tal displays and meter have settled, record the Sodium Digital Concentration Display lents sodium per liter.
1	18.		5 through 17 once. Average the values ob- ort the result as milliequivalents per liter.
	19.	To run the nex	t sample repeat steps 15 through 18.
×	20.	14 but do not a standard has di	ately four samples, repeat steps 8 through adjust the displays. If the high level rifted more than approximately <u>+</u> 0.8 meq./1., epeat the samples previously run.
	21.	To shut down the	he instrument, see Section IV.
I	Γ.	Manual Dilution	n with Indirect Results
	Α.	Reagents: Same	e as I
	в.	Standards: San	ne as I
2	с.	Sample Preparat	tion: Same as I
	D.	Method of Opera noted below	ation: The operation is identical except as
			st the display to an arbitrary number and
		Step 14. Record	d the value of the Sodium Digital Concentration
		Step 17. Recor	olay. d the value of the Sodium Digital Concentration
	•		nterpretation of Results for calculations.
			Page 6 of 11 pages
			AP000680

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rmour Pha	rmaceutical Compar	APC METHOD No. 1301	
		APC METHOD No	- 1
	ITY STANDARDS kakee, Illinois	SODIUM AND POTASSIUM DETERMINATIONS Using the Instrumentation Laboratory Model 343 Flame Photometer	
ANALY	TICAL METHOD	•	
III.	Automatic Di	lution with Direct Results	
Α.	Reagents:		
	l. Lithium Use as r	Stock Concentrate: Use IL Cat #35003 only. eceived.	
в.	Standards:		
	1. Sodium/P	otassium Standards: Use only the IL Calibration	
	Standard a. Sodi	s listed below. um Analysis: Use Sodium Standards 140 meq./l. . #35140) and 100 meq./l. (Cat. #35100)	
1 8		ssium Analysis: Use Potassium Standard 5 meq./1 . #35140) and 2 meq./1. (Cat. # 35120)	-
с.	Sample Prepa using this m	ration: NOTE: N.S.A. can not be reliably perfo	rme
		amples: Reconstitute according to the specifi- and then use the resulting solution.	
r	any cel be allo	rum and related samples: Use as received. If ls or other material are present, they must not wed to enter the dilutor. If the sample is ed, the results may differ from the true value.	
	3. Other sam	mples: Seek qualified assistance.	
D.	Method of Ope	eration - Refer to Figures 1, 2, 3, & 4.	
	1. Refer to	Section IV for instrument start up and ignition	
	rinse so. ficient	h that the bottles containing diluent water, Lution and Lithium Stock Concentrate have suf- volume. There should be at least 5 liters of h water in the diluent reservoir.	
1		the dilutor and make certain that the sample vaining properly.	
	4. Leave the 15 second	e sampling tube in the flushing cup for about ds.	
	wiper (i.	ne sampling tube and wipe it using a lint free e. Kim-Wipes). Allow it to remain out of for 10 seconds.	
24.1	5. 	Page 7 of 11 pages	
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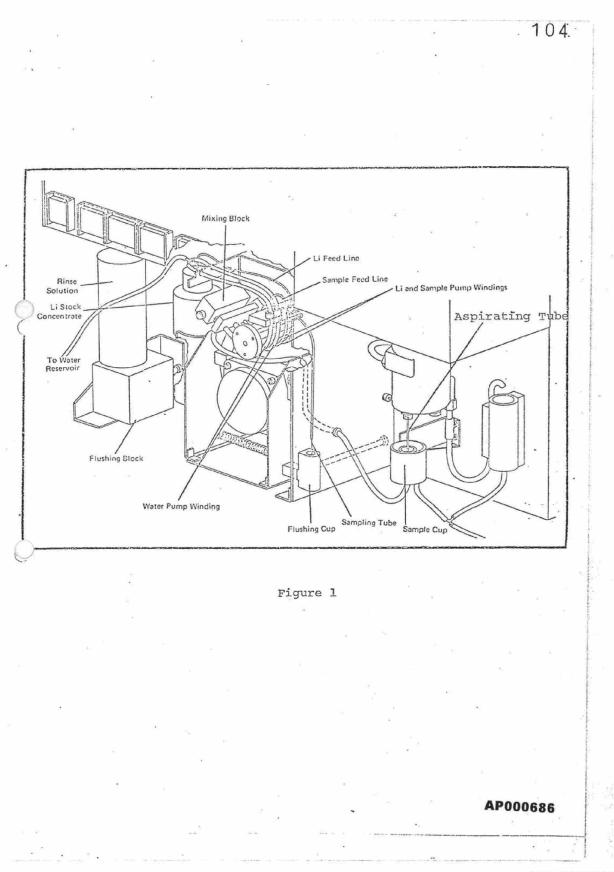
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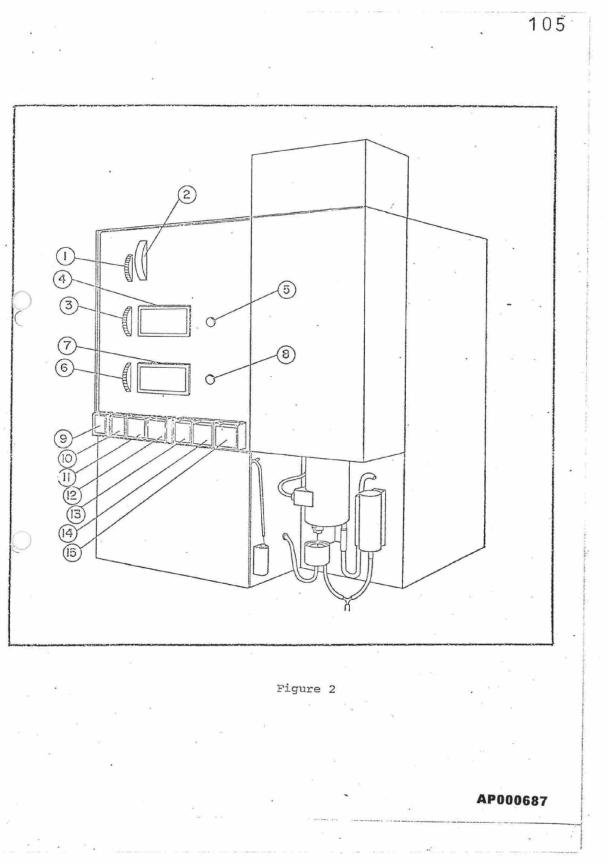
	accutical Company	APC METHOD No
Kenkokee, Illinois		SODIUM AND POTASSIUM DETERMINATIONS Using the Instrumentation Laboratory Model 343 Flame Photometer
ANALYTI	CAL METHOD	NI. A
	DD water. Aft meter have set needle (No. 2	oling tube into a sample cup containing er the digital displays and Lithium tled, set the Lithium Response Meter on figure 2) at the triangle (See figure 4) dium Set Control (No. 1 on figure 2).
	(No. 4 in figu in figure 3).	ium Digital Concentration Display to 000.0 re 2) using the Sodium Zero Control (No. 16 Operate the Sodium Decimal Position Button re 2) to place the decimal point at the n.
	on figure 2) t (No. 17 on fig	assium Digital Concentration Display (No.7 o 00.00 using the Potassium Zero Control ure 3). Operate the Potassium Decimal Position on figure 2) to place the decimal point at the n.
		pling tube and wipe using a lint-free wiper o remain out of solution for about 10 seconds.
	the Lithium me and Potassium values (as dic using the Sodi Potassium Bala if a sodium st	ling tube into the standard solution. After ter and displays are settled, adjust the Sodium Concentration Digital Displays to their proper tated by the standard solution being used) um Balance Control (No. 3 on figure 2) and nce Control (No. 6 on figure 2). For example, andard of 140 meq/liter is being used, adjust play to 140.0.
		pling tube from the standard and wipe it, ree wiper. Allow it to remain out of solution
	there for 10 s	ling tube in the flushing cup and leave it econds. Remove it, wipe with a lint-free wiper o remain out of solution for 10 seconds.
		ling tube into the midrange sodium standard. lays have settled, record the value from the
€ ¥ ×	+ 1 meq/lit the higher lev	ue for the sodium standard should be within er of the label value. If it is not, recheck el standard and reset if necessary. If this ct the problem, seek qualified assistance.
	(allowing an a	cedure for the midrange Potassium Standard ir & rinse flush between standards as per . It should be within \pm 0.1 meq./liter.
- 6600		Page 8 of 11 pages . AP000682

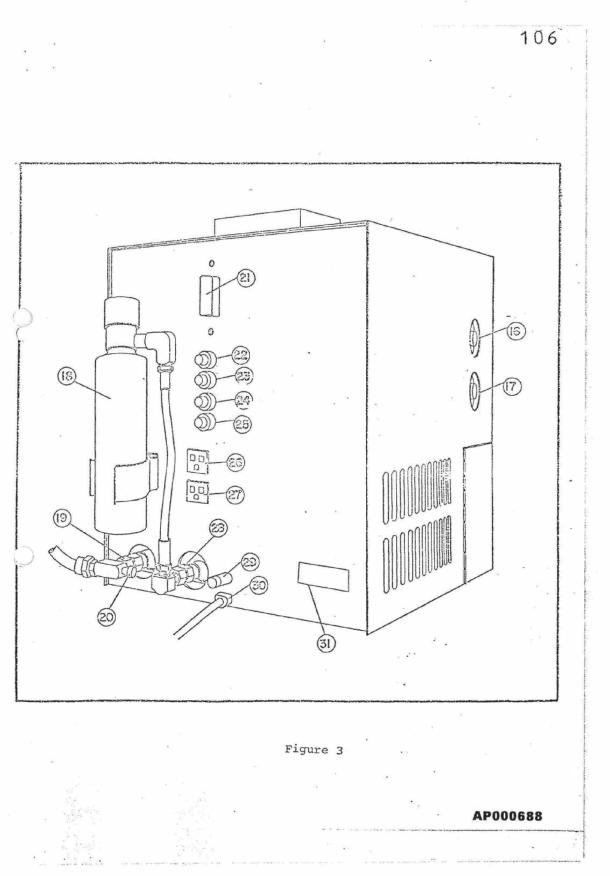
1			AP000683
		-	Page 9 of 11 pages
			gas cylinder replacement. For other problems, fied assistance.
	14i	problem mu	AIR and/or NO GAS lights turn on, this st be corrected. Consult the instruction
		_	oise will be heard.
		come on wi	POWER button. The FLAME ON light should thin 10 seconds. During this time, a
		Adjust the outlet of	regulator to 30 - 40 psi. Open valve at regulator (if so equipped).
		2. Open the m	ain valve on the cylinder of compressed air.
)°		cylinder (ropane Gas Valve at the top of the fuel No. 18 on figure 3) 2.5 counterclockwise turns. uld be felt at the end of the rotation.
		place.	
	Α.	sufficient gas	on: The flame is automatically ignited when and air pressures are available. Do not strument without the Flame Housing Cover in
I		trument Operati	
		*	
	20.	To shut down t	the instrument, see Section IV.
Ĩ		has drifted mo	ust the displays. If the high level standard ore than approximately + 0.8 meq. Na/l (or 0.08 me it and repeat the samples previously run.
		After approxim	nately four samples, repeat steps 9 through 13
2	18.	1	at sample, repeat steps 14 through 17.
1	17.	Repeat steps] and report the	4 through 16 once. Average the results obtained
	16.		oling tube into the sample. After the displays record the values from the display.
	10.	there for 10 s	seconds. Remove it, wipe with a lint-free ow it to remain out of solution for 10 seconds.
	15.	*	emain out of solution for about 10 seconds.
	14.		mpling tube and wipe using a lint-free wiper.
	ANALYT	ICAL METHOD	
	Kank	okee, Illinois	Using the Instrumentation Laboratory Model 343 Flame Photometer
	QUALITY STANDARDS		SODIUM AND POTASSIUM DETERMINATIONS
Armo	our Phari	maceutical Company	APC METHOD No. 1301

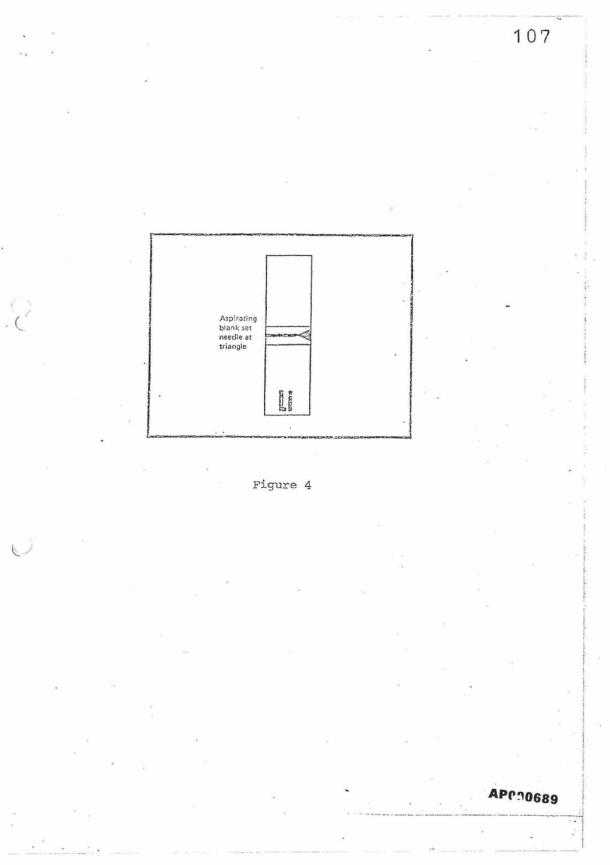
Armou	r Phar	maceutical Company	APC METHOD No
		ITY STANDARDS sokee, Illinois	SODIUM AND POTASSIUM DETERMINATIONS Using the Instrumentation Laboratory Model 343 Flame Photometer
1	NALY	TICAL METHOD	·
	5.	Allow the inst	rument to warm up for approximately 20 minutes.
	6.	under the aspi dilutor and ma	this period, place the sample cup in position rating tube. (see figure I). Turn on the ke certain the drain is operating. Make is at least 5 liters of water in the reservoir.
	7.	Place the samp	ling tube in the flushing cup.
	8.	uniformly wet	es, check the atomizing chamber. It should be without a large amount of droplets visible. If isible, seek qualified assistance.
	9.	after turn: b. Place a dil approximate	sampling cup and store in an unused area ing off the dilutor. luted sample under the aspirating tube for ely 2 minutes. The atomizing chamber should niformly wetted. If so, proceed as under
	10.	two minutes	Dilution Assays sampling tube into a sample for approximately s. The atomizing chamber should still be wetted. If so, proceed as under Section III.
в.	Shu	tdown	
Ĩ	1.	agent (IL Cat #	h automatic dilution assay, draw cleaning #33104) through the dilutor for 30 seconds to and other material from the pump tubing.
	2.	and allow it to position under	, place the sampling tube in the flushing cup o remain there. Place the sample cup in the aspirating tube. Turn on the dilutor d check for proper drain operation.
	з.		ately five minutes, turn off the dilutor. ole cup from under the aspirating tube and used location.
	4.		zing chamber is dry (5-10 minutes), turn off op of the propane cylinder. (2.5 turns
	5.	After the FLAME supply valve of	E ON lamp turns off, close the compressed air Ff.
•			
			Page 10 of 11 pages
			AP000684

Arr	nour P	harm	aceutical Company	APC	1301 No	
			CSTANDARDS ee, Illinois	SODIUM AND POTASSIUM DE Using the Instrumentat Model 343 Flame Photom	ion Laboratory	
	АИА	LYTI	CAL METHOD		· ·	
	в.	Shutdown Continued.				
			. Turn off the power by pushing the POWER button. After 30 seconds, the instrument will shut down.			
	1	 Release the air pressure by removing and then replacing the fitting on the air supply hose. 				
	c. 1	Preventive and Corrective Maintenance.				
Ç	-	l. Refer to the Operation Manual and/or seek qualified				
1	INTERPRETATION OF RESULTS					
	I	A. Calculations for direct results for A.H.F. and N.S.A. samples and all automatic dilution samples.				
	No calculations are required.					
			,	x+		
	E	B. <u>Calculations for Indirect Results</u>				
		0	curve by p	data from the standards, draw plotting the Display value (y ion of the standards (before) versus the	
C/	4 5	 Using the standard curve, determine the values of the samples. Average the replicates for each sample and report those results. 		values of the ch sample and		
		. :		results will be obtained only is followed exactly as writter		
1	REFERENCES					
		 "Operation Manual for the Model 343, Digital Flame Photometer" Instrumentation Laboratory, Inc. Lexington, Mass. (1975) Armour Notebook #K901. 				
	2	. 1	T.WORL NOLEDOO	K #R901.		
				1		
				Page 11 of 11 pages	AP000685	









Armour Pharmaceutical Company	Supplement 2					
QUALITY STANDARDS	Supplement 2 SODIUM & POTASSIUM DETERMINATIONS AHF SAMPLES WITH VARIED RECONSTITUTION VOLUMES					
Konkokee, Illinois						
ANALYTICAL METHOD	PERSEDES:	-				
4/8/78	New	W. H. Osgood				
This supplement describe fill AHF samples reconst reconstituted to 20 ml.	es the sample preparati ituted to 10 ml and do	on required for single ouble fill AHF samples				
Sample Preparation						
	stituted to the volume this into 5 ml volumet water and mix well.					
flask. Pipet 50.0 m	diluted sample into 20 nl of Lithium Internal to the mark with DD wa	Standard into the				
Method of Operation						
Refer to the method.	· ·	: *				
Interpretation of Result	s					
Due to the additiona the display must be original sample.	1 4 to 10 dilution, th multiplied by 2.5 to o	he result obtained from obtain meqNa/l in the				
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) ,						
· ·						
. at						
		· •				
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Armour Di	armanaulical Campany		1.21 N	109	1.
	armaceutical Company LITY STANDARDS			APC METHOD NO. 1344	
ĸ	enkakee, Illinais	DETERMINATI	ON OF FI	IBRINOGEN	1
ANAL	YTICAL METHOD		· • *	•	
3/2	1/7.9	SUPERSEDES:		A. K. ROOD	
		3		ананана и страна и с К	
rea a l by	aliquot of the agent and the ti Fibrometer. Fin		lotting of fibri	is measured using nogen is determined	
COMMEN	rs				
Α.	Safety Precaut	ions			
		tory safety condi-	tions pr	evail.	
в.	General Precau	tions	•		
- 	Any samples from human blood, although nonreactive when tested for hepatitis associated antigen, may still present a risk of transmitting viral hepatitis, as no completely reliable laboratory test is yet available for hepatitis virus.				
MATERIA	LS FOR TESTING			4	
1.	Fibrinogen Ref	erence Standard			
	purchased from (Scientific Pro lyophilized con	inogen calibration Dade Reagents, In oducts, distributo ntents of one 'vial inogen reference m uted.	nc., Mia or). Re with l	mi, Florida constitute the	
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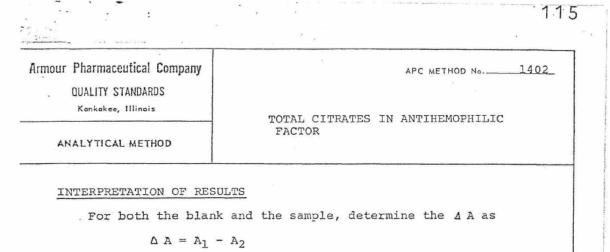
	inaceulical Company TY STANDARDS	APC METHOD No. 1344			
Konk	okce, Illinois	DETERMINATION OF FIBRINOGEN			
ANALY	FICAL METHOD	*			
MATERIA	L FOR TESTING				
(Cont'd	.)				
2.	Bovine Topical	Thrombin (Parke-Davis #4-2076-1)			
)	Reconstitute the contents of 1 vial (1000 NIH units per vial) with 20 ml of 0.9% saline. Divide the solution into 4 ml aliquots, transfer to appropriate size vials, stopper, and store frozen at -20°C. During the assay, keep the thawed working solution in an ice bath. Thrombin obtained from a supplier, other than Parke-Davis, may be substituted.				
3.	Owren's Veronal	Buffer			
	Into a 1 liter beaker containing about 800 ml of distilled water, add 5.855 g of sodium barbital and 7.306 g of reagent grade sodium chloride. Mix until the reagents have dis- solved. Using a pH meter measure the pH of the solution and adjust to pH 7.35 using lN hydrochloric acid. Quanti- tatively transfer the solution to a 1 liter volumetric flask and dilute to volume with distilled water.				
4.	Saline Solution	1			
,		of reagent grade sodium chloride in suffi- water to make 1000 ml.			
5.	Fibro System consisting of a Fibrometer Precision Coagu- lation Timer, a Thermal Prep Block and an Automatic Electric Pipette. The Fibro System may be purchased from BBL, Cockeysville, Maryland. An equivalent unit may be substi- tuted.				
TEST PRO	CEDURE				
1.	of the followin	's Veronal buffer as diluent, prepare each g Reference Standard dilutions just prior to epare all dilutions simultaneously. Assay n duplicate.			
	- continued on	next page -			
		· · · · ·			
8		Page 2 of 3 pages AP000692			

		· · · · · · · · · · · · · · · · · · ·
	Armour Pharmaceutical Company	C METHOD No. 1344
	QUALITY STANDARDS	
-	Konkokee, Illinois DETERMINATION OF FIBRIN	NOGEN
	ANALYTICAL METHOD	*
	- continued from page 2 -	•
	1:20 - 0.1 ml Fibrinogen Ref. Std. plus 1.9 ml	
9	NOTE: Use automatic 2-step pipette gun for acc 200 µl volumes.	urate 100 and
	 Incubate 0.2 ml of the fibrinogen standard sample dilution to be tested) at 37°C for 2 	
	 Add 0.1 ml of thrombin reagent and start th determine clotting time. 	e timer to
	4. Average the duplicate determinations to det clotting time for the dilution being tested deviation for the averaged value should be	. The standard
	5. Based on the expected amount of fibrinogen prepare three dilutions of the sample that clotting times within the range of clotting for the Reference Standard. Use the Verona dilutions and assay duplicate aliquots from by repeating Steps 2, 3, and 4.	will result in times obtained 1 Buffer for all
Ł	L	* ``
Y	INTERPRETATION OF RESULTS	*
	 Plot the Fibrinogen Reference Standard conc clotting time on log - log paper and connec with the best straight line or use a linear analysis. 	t the points
	 By reference to the standard curve calculat ogen in the sample dilution; report as mg f solution. 	e the fibrin- ibrinogen per ml
	REFERENCES	
	Data - FI Fibrinogen Determination, Dade Diagno 1851 Delaware Parkway, Miami, Florida	stics, Inc.,
Y	ř -	
		AP000693
	sd 2/21/79 Page 3 of 3 pages	

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Armour Pharmaceutical Company DUALITY STANDARDS		APC METHOD N	o. <u>1402</u>
Kankakee, Illinois	TOTAL CITRAT FACTOR	ES IN ANTIHEMOPH	ILIC
ANALYTICAL METHOD	JPERSEDES:	PREPARED BY:	
9/5/80	New	L. C	otter
citrate is determ action is monitor . 340 nm due to the dinucleotide, red the extinction co	uted with triple di nined by an enzymati ed by observing the e oxidation of NADH luced form). The ci pefficient of the NA metric with the amou	c reaction. The change in absor (ß-nicotinamide trate is calcula DH since the amo	re- bance at adenine ted from
a. Safety Precau prevail.	tions: General lab	oratory safety c	onditions
citrates. 2. Oxaloacet cator rea free of t only if t	citrates are deter	e substrates for ne sample must b ace levels can b	the indi- e relatively e tolerated
a purchased ki	written in two sect: t (Section I) or pro ction II). It is p	eparing the reag	ents in
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	Page 1 of 6 pages		
ASON FOR REVISION:		GRO-C	9-3-80 9-3-80 9-3-80 9-4-80
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<u>.</u>		· · · ·			
តា០៨		aceutical Company		APC METHOD No.	1402
		STANDARDS			
			TOTAL CITRATE FACTOR	S IN ANTIHEMOPHILIC	
A	NALYTIC	CAL METHOD			(and the first strength stre
I			SING THE CITRIC ACID K bheim Cat. No. 139076)		
M	ATERIA	LS FOR TESTIN	1G		
	А.	Equipment ar	nd Supplies		
		in absor using l	sion spectrophotometer bance capable of oper cm cuvettes (nondispo suitable unit.	ating at 340 nm and	
	•	2. Volumetr	ic Glassware	*	
			: Eppendorf style au ng 20 µl, 100 µl, and		
	в.	Reagents	·	ak *	
		constitu structio and pipe	tired reagents are con the the vials as neede ons for the proper vol ets. The solutions ar cructions and must be	d. Refer to the ki umes. Use distille e stable as describ	t in- d water ed in
ž	с.	Standards			
			e not required, but c analysis. See Method		d to
	D.	Sample Prepa	ration	ιά.	
	."	cation. Aft to 50 ml in	the sample as direct for the sample is in so a volumetric flask us sample is to be run i	olution, dilute 1.0 ing triple distille	ml
	200 00	OCENIIPE		· · · · · · · · · · · · · · · · · · ·	
		OCEDURE			
ż	Α.		trophotometer to 340 : rbance with nothing i: ams.		
	в.	Blank Determ	ination		
			lean, dry 1 cm cuvette llowed by 1.0 ml from		
			Page 2 of 6 pages	AP000	695

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ہ د رائی	·				· · · ·	
Armour Pharmaceutical Company QUALITY STANDARDS					APC METHOD No. 1402	
	Kankaka	ee, Illin		TOTAL CITRATES FACTOR	IN ANTIHEMOPHILIC	
	ARALITIC					
	TEST PF	OCED	URE (Con'	t.)		
	в.	(Coi	n't.)			
		2.		e cuvette in the spectr absorbance, A ₁ , when s	· ·	
e		3.	Mix well	. Follow the change in equilibrium (i.e., the	.020 ml) from bottle #2. absorbance until it has reaction is complete).	
		4.	Repeat st	teps 1 through 3 for a	second blank.	
	с.	Sam	ple Detern	nination		
		1.	Into a clean, dry 1 cm cuvette, pipet 1.8 ml distille water followed by 1.0 ml from bottle #1.			
t		2.		200 µl (0.20 ml) of the . Mix well.	e diluted sample or	
		3.		e cuvette in the spectra absorbance, A _l , when s		
Ó		4.	Mix well.	. Follow the change in equilibrium (i.e., the :	.020 ml) from bottle #2. absorbance until it has reaction is complete).	
		5.	second di		duplicate assay using a t is to be run in dupli- d samples.	
	4) 		2			
					¥	
				• *		
	Ā					
				, ,		
	X			Page 3 of 6 pages	AP000696	



Determine the average \bigtriangleup A for the blank and calculate the \bigtriangleup A_{rp} for the sample as

 $\Delta A_{T} = \Delta A_{sample} - \Delta A_{blank}$

Citrate, $g/L = \frac{3.02 \times 191.1}{6.3 \times 1.0 \times 0.2 \times 1000} \times A_T \times Dilution Factor$

Citrate, mm/L = $\frac{3.02}{6.3 \times 1.0 \times 0.2} \times \Delta A_T \times Dilution Factor$

II. DETERMINATION USING REAGENTS PREPARED IN LABORATORY

MATERIALS FOR TESTING

- A. Equipment and Supplies -- (Same as Section I)
- B. Reagents

Use reagent grade chemicals or better. The term water means the use of distilled water.

1. TEA Buffer with Zn, 0.1M, pH = 7.8: Weigh out 14.9 g of triethanolamine and dissolve in approximately 800 ml water. Adjust the pH to 7.8 ± 0.05 using dilute hydrochloric acid (1N or 10%). Add 28 mg of zinc chloride and mix well. Dilute to 1000 ml and mix.

2. NADH, 6mM: Weigh out 25 mg of /3 -Nicotinamide adenine dinucleotide, reduced, disodium salt (Boehringer Mannheim Cat. No. 107727 or equivalent) and 50 mg of sodium bicarbonate into a 5 ml volumetric flask. Dissolve the solids in water and dilute to the mark. Mix well. Kept refrigerated (2-8°C), this reagent is stable for about 1 day. Make fresh daily as needed. (Keep protected from light).

	Page 4 of 6 pages	AP000697	
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	ар Ларинан Х.Таналага, Каланар на 1,5,7,2, Даринанан тарар Бала Харанар Аналага на (д. 1999). 1		
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Armou	r Pharma QUALITY		al Company ARDS	-		APC ME	THOD No. 14	102
	Kankaka			тс	OTAL CITRATE	S IN ANTIH	EMOPHILIC	
4	NALYTIC	CAL ME	THOD	F	FACTOR			
1	MATERIA	LS F	OR TESTIN	g (Con't.)				
	в.	Rea	gents (Con	n't.)				
9		3 -	hydrogen No. 1272 hydrogen No. 1272 0.4 ml o:	ase (6000 48 or equi ase (5500 21 or equi f TEA Buff	ivalent) and	Soehringer M 0.5 ml of Soehringer M So a small of A). This so	Mannheim Cat. lactate de- Mannheim Cat. container. <i>P</i>	
•,	÷	4.	103365. amount ec protein)	Dissolve quivalent in 1 ml i stable for	to approxim tce-cold dis	5) of lyoph ately 5 mg tilled wate	nilizate (an	ı ı–
	с.	Sam	ple Prepar	cation	(Same as Se	ction I)		
	TEST PR	OCED	URE			· · · ·		
<u> </u>	Α.	Set to	the spect	bance wit			ist the unit ne sample or	
<u> </u>	в.	Bla	nk Determ	ination				
		1.	Into a cl order:	lean, dry	cuvette, pi	pet the rea	igents below	in
			بر 100 1بر 20	nl of TEA 11 NADH 1 Dehydrog 11 distill	genase mixtu	re		
	4	2.			in the spec ce, A ₁ , when		cer and deter	-
		з.	lyase and until it	l mix well	. Follow t	he change i	of the citra n absorbance the reaction	
		4.		122	ough 3 for	a second bl	ank deter-	
			mination.	Page 5 of			AP000698	

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· · · · · · · · · · · · · · · · · · ·		7
our Pharmaceutical Company QUALITY STANDARDS	APC METHOD No. 1402	
Konkokee, Illinois	TOTAL CITRATES IN ANTIHEMOPHILIC FACTOR	
ANALYTICAL METHOD		
TEST PROCEDURE (Con	't.)	
C. Sample Deter	rmination	
	clean, dry cuvette, (nondisposable) pipet the ng in order:	
100 20 j	ml TEA Buffer µl NADH µl Dehydrogenase mixture µl diluted sample (or standard)	e olean e ren a deeparte, se
	he cuvette in the spectrophotometer and deter- e absorbance, A_1 , when stable.	
lyase an until i	nto the cuvette 20 µl (0.020 ml) of the citrate nd mix well. Follow the change in absorbance t has reached equilibrium (i.e., the reaction lete). Record A ₂ .	· · · · · · · · · · · · · · · · · · ·
sample	steps 1 through 3 for duplicate assays. Each is to be assayed in duplicate using two different samples.	
INTERPRETATION OF RI	ESULTS (Same as Section I)	E.
REFERENCES		
	t al "Fluorometry of Citrate in Serum with the ate (pro-3S) lyase", Clin Chem <u>21</u> , 730-734 (1975)	
	Enzymology, J.M. Lowenstein, Ed. Vol XIII Aca- , 1969, pages 517-518	
3. Methods of H 76/77	Enzymatic Food Analysis, Boehringer Mannheim	
4. Armour Metho	ods 1303, 1390, 1392, and 1393	
5. Armour Noteb	book K895, pages 290 and 291	
	2. Aldred on validation of enzymatic method sh Pharmacopeia method as referee	
7/8/80 dw		
	Page 6 of 6 pages	

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		e	
Armour Pharmaceutical Company		. APC METHO	D NO1410
QUALITY STANDARDS Konkokee, Illinois	SURFACE ANT		II-Elec-
ANALYTICAL METHOD	tro-Nucleon	ics Laboratorie	s, Inc.)
7/10/80	SUPERSEDES: New	PREPARED BY:	K. Roop
TEST SUMMARY	1		
detection of HB _s . body to Hepatiti the indicator. Anti-HB _s (Goat) particles in tab is added to the cubation the tab Antigen is prese with the antibody tion, the serum	solid phase radioim Ag which employs Iod s B Surface Antigen The test employs the is coated to control let form (solid phas tube containing a CP let disintegrates. Int in the serum test y on the glass parti is removed and the g ed antibody specific	ine-125 labeled (Goat) (Anti-HB "sandwich tech led pore glass e). Patient se G tablet. Duri If Hepatitis B ed it will comb cles. After in lass beads rins	Anti- s) as nique". (CPG) rum ng in- Surface ine cuba- ed.
antibody on the The 1251 labeled in a gamma count qualitative test antigen in serum	body combines with t glass particles form antibody is the ind er. The radioimmuno for the presence of . In general, howev in a sample, the gre	ing the "sandwi icator which is assay for HB _S Ag Hepatitis B Su er, the greater	ch". detected is a rface the
COMMENTS	, · · · ·	× * 9	
Safety Precaution			
l. Handle all rettitis. Mouth	eagents as if capable pipetting of reage	nts and samples	must
be avoided. should be wor	Rubber gloves and parts	rotective cloth	ing
÷	Page 1 of 10 page	ges	
SON FOR REVISION:		GRO-C	6-30-80
in and a second s		GRO-C	7-2-80
*		GRO-C	7-8-80
	ing and the second	GRO-C	7-10-80
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Armour Pharmaceutical Company DUALITY STANDARDS

APC METHOD No. 1410

RIAUSURE II ANTIBODY TO HEPATITIS B SURFACE ANTIGEN (RIAUSURE II-Electro-Nucleonics Laboratories, Inc.)

ANALYTICAL METHOD

Konkokee, Illinois

Safety Precautions (Continued)

- 2. All materials used in this assay including reagents and samples should be disposed of in a manner that will inactivate human hepatitis virus. The preferred method is autoclaving for 60 minutes at 121°C. The liquid waste may be decontaminated by addition of a mixture of 20 ml of formalin and 60 ml of acetic acid per liter or sodium hypochlorite (bleach) 2.5% in the final volume. The waste should be allowed to stand overnight to inactivate the virus before disposal.
 - Eating, storing or preparing of food, smoking or applying cosmetics is banned in all areas where radioactive materials are stored or used.
 - Direct contact with radioactive materials must be avoided by using protective laboratory coats, wearing disposable plastic or rubber gloves and employing safety pipettes.
- All spills of radioactive materials must be reported to the person in charge and decontaminated immediately. Contaminated wastes should be discarded with solid radioactive waste.
- 6. Current Federal Nuclear Regulatory Commission regulations allow for disposal of small quantities of labeled material, ¹²⁵I as in this kit, via the normal sewer system. Disposal by flushing should be restricted to sinks in authorized areas and limited to a few microcuries per day with adequate water flow.
- Sterilized solid waste may be disposed of by conventional means. Consult the applicable regulations of Title 10, Code of Federal Regulations, Part 20 and local or State regulations.
- 8. WARNING: All samples should be treated as if capable of transmitting hepatitis. The precautions given above should be strictly observed.

General Precautions:

DI - 6600

1. All reagents should be brought to room temperature before use.

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Page 2 of 10 pages

Armour Pharmaceutical Company QUALITY STANDARDS

Konkokee, Illinois

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APC METHOD No. _____ 1410_

RIAUSURE II ANTIBODY TO HEPATITIS B SURFACE ANTIGEN (RIAUSURE II-Electro-Nucleonics Laboratories, Inc.)

ANALYTICAL METHOD

General Precautions (Continued)

2. Insufficiently clotted plasma specimens are often responsible for false positive reactions in the RIA assay due to the presence of fibrin strands. Samples which contain fibrin strands should be heated at 56°C. for 20 minutes, the fibrin clot sedimented by centrifugation at 10,000 x G and the supernatant used for testing.

3. For patients receiving heparin therapy, such as those undergoing renal dialysis, blood for HB_SAg screening should be drawn before therapy is started. Blood drawn after therapy has started may clot in the RIAUSURE reaction tube causing a spurious result.

- 4. If samples are to be stored, care should be taken to maintain sterility. Sodium azide, to a concentration of 0.1%, may be added to preserve sterility. Store at 2° to 8°C.
 - Samples contaminated with microorganisms may also be unsuitable; care should be taken to preserve the sterility
 of samples.
- 6. A sample is non-reactive for HB_SAg if the ratio of the counts per minute (CPM) divided by the mean CPM of the negative control does not exceed an established cutoff ratio. Such a serum may considered to be non-reactive for Hepatitis B Surface Antigen and need not be tested further.
- 7. A serum is reactive for HB_SAg if the ratio exceeds the established cutoff. Because of the greater immunologic sensitivity of radioimmunoassay, false positive reactions are a possibility. For this reason, each reactive serum must be confirmed as positive for Hepatitis B Surface Antigen by a specificity test. Two classes of false positive reactions occur: 1) a nonrepeatable positive, due to technical error in testing, such as inadequate washing; 2) a repeatable positive which cannot be confirmed by specificity testing. The presence of Hepatitis B Surface Antigen may be confirmed by a specificity test which uses human Antibody to Hepatitis B Surface Antigen to neutralize the antigen in the sample. A small number

- continued on next page -

Page 3 of 10 pages

AP000702

Armour Pharmaceutical Company QUALITY STANDARDS APC METHOD No. 1410

RIAUSURE II ANTIBODY TO HEPATITIS B SURFACE ANTIGEN (RIAUSURE II-Electro-Nucleonics Laboratories, Inc.)

ANALYTICAL METHOD

Konkokee, Illinois

General Precautions

7. (Continued from preceding page)

of samples--usually less than 1 out of 10,000--will be repeatably positive but not confirmed by the specificity test. A reactive sample may be confirmed by a less sensitive test such as Counterelectrophoresis (CEP), or Agar Gel Diffusion (ADG). However, if there is disagreement between the two tests, the RIA specificity test must be performed. A specificity test to confirm the presence of Hepatitis B Surface Antigen in serum is available from Electro-Nucleonics Laboratories, Inc.--RIA-FIRMTM Specificity Test for Hepatitis B Surface Antigen.

MATERIALS FOR TESTING

A. RIAUSURE II Test Kit (100 tests), List No. 3910

Kit Contains:

DI-6600

100 reaction tubes (5 cards of 20 tubes each) each containing a CPG tablet coated with Antibody to Hepatitis B Surface Antigen (Goat) and a magnetized ferrite rod as a mixing device. 1 vial (10 ml) Antibody to Hepatitis B Surface Antigen ¹²⁵I (Goat); each vial contains less than 10 microcuries; perservative 0.1% sodium azide.

1 vial (5 ml) Negative Control (Human serum non-reactive for $HB_{\rm S}Ag$); preservative 0.1% sodium azide.

1 vial (2 ml) Positive Control (Human serum positive for $HB_{\rm s}Ag$); preservative 0.1% sodium azide.

l vial Buffer Powder. Dissolve the contents of the vial in l liter of distilled or deionized water. The dissolved buffer is a 0.01M phosphate buffer (Na_2HPO_4/NaH_2PO_4) containing 0.15M NaCl. The pH should be 7.4 ± 0.2 units.

B. Magnetic Agitating Table (MAT) consisting of a controller and a Reaction Table. The reaction table holds 100 tubes in cards. The principles of operation of the MAT are included in the operating instructions for the instrument.

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*	aceutical Company	APC METHOD No. 1410
Konkak	Y STANDARDS	RIAUSURE II ANTIBODY TO HEPATITIS B SURFACE ANTIGENT (RIAUSURE II-Elec- tro-Nucleonics Laboratories, Inc.)
MATERI	ALS FOR TESTING	G (Continued)
	Wash Systems	
	1. Single Wa	ash Devices
		vice for delivering 1.0 ml of Buffer Solution.) ml Cornwall syringe is suitable.
0	b. A was	sh cannula for attachment to the delivery device.
•	. react	piration cannula for removal of buffer from the tion tubes. A vacuum source for use with the that is required.
	2. Multiple	Wash Devices
	at th priat	ti-wash unit which washes 10 reaction tubes the same time. This must be used with an appro- te dispensing system capable of delivering to of buffer (1.0 ml per tube).
	tubes	ti-aspirator unit which aspirates 10 reaction at one time. A vacuum source for the multi- ator is required.
Q.	ma to so . su th	e aspiration cannula or multi-aspirator unit y be attached to a suitable vessel connected a trap which in turn is connected to a vacuum urce. The collection vessel should contain fficient disinfectant solution to inactivate e Hepatitis virus such as sodium hypochlorite .5% solution final concentration).
D.	Pipettes capa	ble of accurately delivering 0.1 and/or 0.2 ml.
E.	Wash dispensi matic syringe	ng devices, such as Repipet or Brewer auto- s.
F.	Counting tube	s for Gamma Counter.
G.	Gamma Counter 125Iodine. (I 50% or greate	capable of counting the weak gamma photon of t is recommended that the counter efficiency be r.)
		Page 5 of 10 pages AP000704

Armour Pharmaceutical Company

APC METHOD No. 1410

QUALITY STANDARDS

Kankakee, Illinois

ANALYTICAL METHOD

RIAUSURE II ANTIBODY TO HEPATITIS B SURFACE ANTIGENT (RIAUSURE II-Electro-Nucleonics Laboratories, Inc.)

TEST PROCEDURE

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A. Regular Assay

Three positive and seven negative controls should be included in each run regardless of the number of samples to be tested. The control must be tested at the same time as the unknown samples using identical reagents and procedures.

- Place the cards with reaction tubes on the MAT. Carefully remove the strip cap. It is best removed by upward pressure at the sides of the tubes. Do not pull the strip from an end as this method tends to expel tablets from the tubes.
- 2. To each of the required and appropriately identified reaction tubes add 0.2 ml of either patient specimen (serum or plasma), Negative Control or Positive Control using a precision pipette. <u>Caution</u>: A new disposable tip must be used for each sample.
- 3. On the Controller, push the switch marked SAMPLE. The switch lamp will light and a series of agitation/setting cycles will begin. At the end of 24 such cycles (one hour) the sample incubation time is complete. At this time, the lamp in the SAMPLE switch will be extinguished. The Light Emitting Diode (LED) counter will display the number 24. At this stage the test samples may be allowed to stand up to 18 hours before proceeding with rinsing and addition of labelled antibody without significant alteration of results.
- 4. Add 1.0 ml Buffer Solution to each of the tubes.
- 5. On the Controller, push the switch marked WASH. The switch lamp will light up and a single cycle of 60 seconds Agitation and 90 seconds Settle will begin. When the cycle is complete, the lamp in the switch will be extinguished and the LED counter will show (1).

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AP000705

Armour Pharmaceutical Company

QUALITY STANDARDS

Kankakee, Illinois

RIAUSURE II ANTIBODY TO HEPATITIS B SURFACE ANTIGEN (RIAUSURE II-Electro-Nucleonics Laboratories, Inc.)

APC METHOD No

ANALYTICAL METHOD

TEST PROCEDURE

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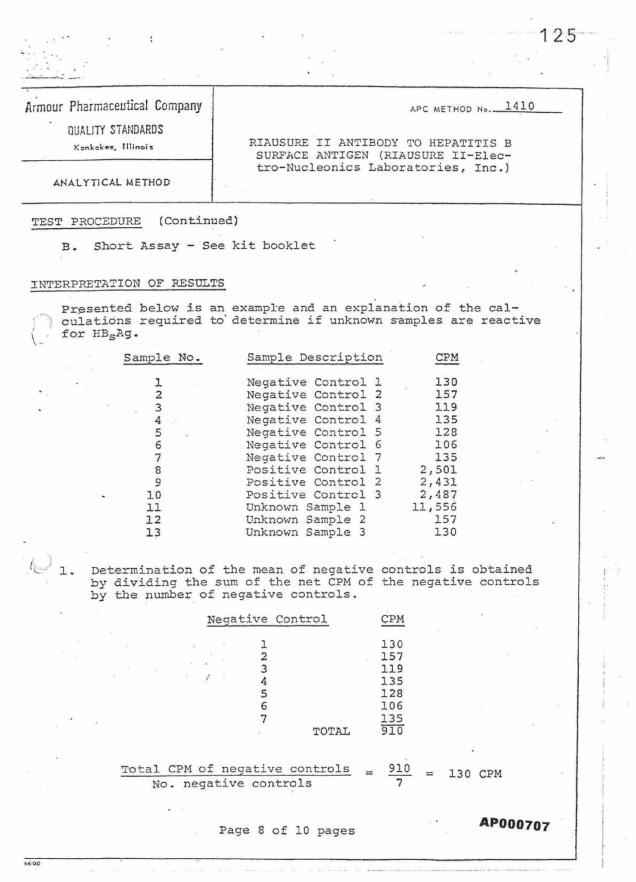
A. Regular Assay (Continued)

 Aspirate the contents of each tube allowing for 3-4 mm above the settled CPG glass.

- <u>NOTE</u>: Care should be exercised when aspirating fluid from the reaction tube. Excessive vacuum will cause stirring of the settled CPG and aspiration of particles. Aspiration of CPG will give spurious low CPM. With the 10-place aspirator only a few inches of vacuum is required.
- 7. Carefully add 0.1 ml of the 1251 labeled antibody to each tube. Direct the flow to the bottom of the tube. Do not allow the tip of the delivery pipette to touch othe upper part of the tube.
- 8. On the Controller, push the switch marked LABEL. The switch lamp will light and a series of agitation/settling cycles will begin. At the end of 24 such cycles (one hour), as indicated on the LED counter, the incubation is complete and the lamp in the LABEL switch will be extinguished.
- 9. Aspirate the contents of the tube allowing for 3-4 mm of liquid above the settled CPG glass particles.
- 10. Add 1.0 ml Buffer Solution to each tube.
- 11. On the Controller, push the switch marked WASH. The switch lamp will light and a single cycle of 60 seconds Agitation and 90 seconds Settle will begin. When the cycle is complete, the lamp in the switch will be extinguished and the LED counter will display a (1).
- 12. Aspirate the Buffer Solution from each tube.
- 13. Repeat steps 10, 11 and 12 three more times for a total of four washes as shown on the LED counter.
- 14. Remove the reaction tubes from the cards and place in counting tubes.
- Count the radioactivity in each reaction tube for 300 seconds with a suitable well-type gamma scintillation counter.

AP000706

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rmour Pharmaceutical Company	APC METHOD	No. 1410
QUALITY STANDARDS Konkokee, Illinois	RIAUSURE II ANTIBODY TO HEPATI SURFACE ANTIGEN (RIAUSURE II- tro-Nucleonics Laboratories,	Elec-
ANALYTICAL METHOD		·
INTERPRETATION OF RESU	LTS (Continued)	-1
	al negative control values falling o to 1.5 times the negative control me	
Ó Þ	0.5 x 130 = 65 1.5 x 130 = 195 cceptable Range - 65 CPM to 195 CPM	·
In the above, i	no negative is rejected as aberrant.	·. 1
negative contro 0.5 and 1.5 tin aberrant negati	ontrol need not be revised. Normall, ol values should fall within the rand mes the control mean. If more than ive control value is consistently de must be suspect and the problem invest	ge of one tected,
at least 5 time	the mean of the positive control she es the mean of the corrected negative echnique must be suspect and the run	e con-
	Positive Control CPM	й.
	1 2,501 2 2,431 3 2,487 TOTAL 7,419	
	$\frac{\text{of positive controls}}{\text{ositive controls}} = \frac{7,419}{3} = 2$,473 CPM
	$\frac{1 \text{ of positive control}}{1 \text{ of negative control}} = \frac{2,473}{130} = \frac{1}{130}$	19.0
This ratio indi the data valid.	icates that the technique is acceptal	ole and
5. Calculation of	the cut off value:	(
A. Multiply th 2.0. For	ne net CPM of the negative control me Example: 130 x 2.0 = 260 CPM	an by
	Page 9 of 10 pages	в
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mour Pharmaceutical Company	A	PC METHOD No. 1410			
QUALITY STANDARDS Konkokee, Illinois	RIAUSURE II ANTIBODY TO HEPATITIS B SURFACE ANTIGEN (RIAUSURE II-Elec-				
ANALYTICAL METHOD	tro-Nucleonics Laboratories, Inc.)				
INTERPRETATIONS OF RE	ESULTS (Continued)				
example i	alated cut off for positive ts 260 CPM. Therefore, all cceeding 260 net CPM must be HB _S Ag.	specimens in this '			
For Examp	ole:	*			
Unkn	Nown Sample 111,556 CPNown Sample 2157 CPNown Sample 3130 CP	M			
fo An ba	ny gamma counters do not ha or automatically subtracting alternative to manual subt ckground from each sample i e negative control as illus	the background CPM. raction of the s to recalculate			
	of the Negative Control Me t Background	an = 160 CPM = 30 CPM			
(160 - 30	x 2.0 + 30 = 290 CPM				
	, specimens exceeding 290 g eactive for HB _S Ag.	ross CPM are con-			
the cut off v reactive for 1	es cited, sample #1 with 11 alue of 290 CPM and is there HB _S Ag. Samples #2 (157 CPM the cut off value and are for HB _S Ag.	efore considered) and #3 (130 CPM)			
RIAUSURE DURE, Spec	st is referred to the bookle II Test Kit for Limitations cific Performance Character: lists of References.	of the TEST PROCE-			
REFERENCE		5. J			
Electro-Nucleonic: Booklet.	s Laboratories, Inc. RIAUSU	RE II Test Kit			
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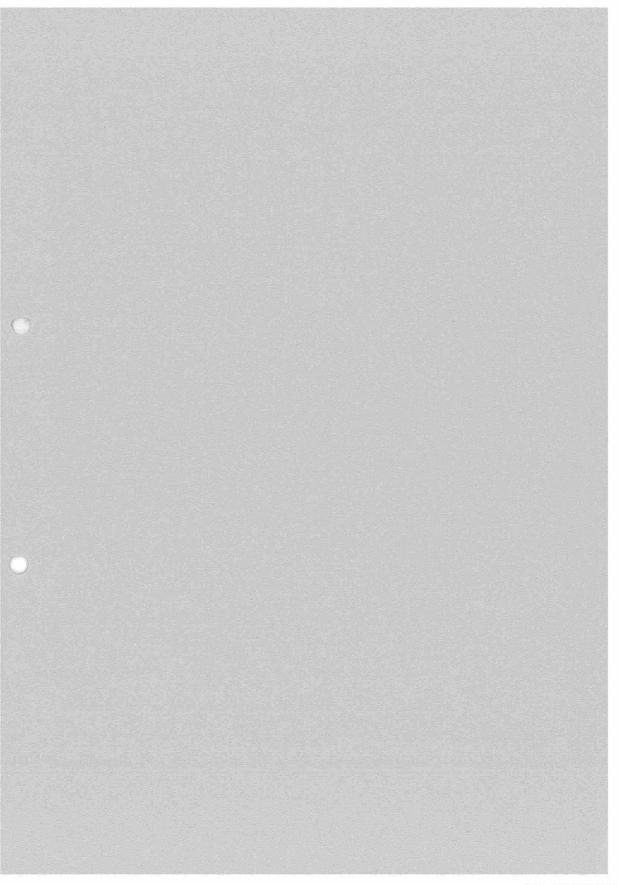
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APPLICATION FOR A PRODUCT AUTHORISATION FOR

HIGH POTENCY FACTORATE

PAGE NO.

PART III	PRECLINICAL/EXPERIMENTAL STUDIES								129
PART IV	HUMAN PH PHARMACI		and the state						130
PART V	CL1	ENICAL	. TRIA	<u>\LS</u>					135
	SUMMARY	•••	••	k	• •				135
	STUDY 1	•••	••		••		••		142
	STUDY 2	•••	-	••	••	••	• •		164
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	STUDY 4	••		••			••	••	196

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PART III

PRECLINICAL/EXPERIMENTAL STUDIES

High Potency Factorate is an Anti-haemophilic Fraction used in the treatment of classical haemophilia A or hereditory disease manifested by deficiency of circulating Factor VIII. Factorate products are rich in this Factor which has been isolated from human plasma and the rationale for treatment is the replacement of this blood clotting factor. Consequently Preclinical/Experimental studies in respect of pharmacodynamics, pharmacokinetics and toxicity have not been presented here because:

- (a) The material is a protein of human origin and toxicological studies in animal species would be inappropriate.
- (b) High Potency Factorate is administered by intravenous injection/ infusion to the site of action which is the circulatory system and pharacokinetic parameters are thus of reduced importance.
- (c) The product is identical to the endogenous circulating Factor VIII and is distributed and eliminated by the same pathways.

Each batch of product is tested for presence of foreign (non-human) proteins and for abnormal toxicity.

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PART IV

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HUMAN PHARMACODYNAMIC AND PHARMACOKINETIC STUDIES

The pharmacokinetic profile of High Potency Factorate (batch K852020) after intravenous injection in human patients has been evaluated by Dr. P. H. Levine, Professor of Medicine at University of Massachusetts Medical School. A copy of his letter to the Company with graphical

representations of his results are presented overleaf. The patient records associated with this investigation are incorporated in the Clinical Section of this documentation as part of Dr. Levine's clinical trial. In this study the levels of product in the circulation are represented by increase in the levels of circulating Factor VIII measured by clinical assay.

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ARMOUR000920

ARMO000092_0134

The Memorial Hospital 119 Belmont Street Vorcester Massachusetts 01605 (617) 793-6611

February 1, 1978

Dr. Carroll O. Johnson Senior Clinical Research Associate Armour Pharmaceutical Company Greyhound Tower Phoenix, Arizona 85077

Dear Dr. Johnson:

Enclosed are six sets of data with regard to our trial of your new Factor VIII preparations AL-1259 (lot number 852030). We are returning any remaining unused material to you under separate cover.

As you will note from the enclosed data, we found your AHF to produce excellent yields as determined by in vivo assay. After the initial rapid fall-off seen after injection of all Factor VIII preparations, your material exhibits a half-life in the circulation in the range of 8 - 12 hours. It would appear to be better than average for a product of this type.

Sincerely yours,

GRO-C

Peter H. Levine, M.D. Chief, Medical Division Professor of Medicine, U. Mass. Medical School Director, New England Area Comprehensive Hemophilia Center

PHL:cem

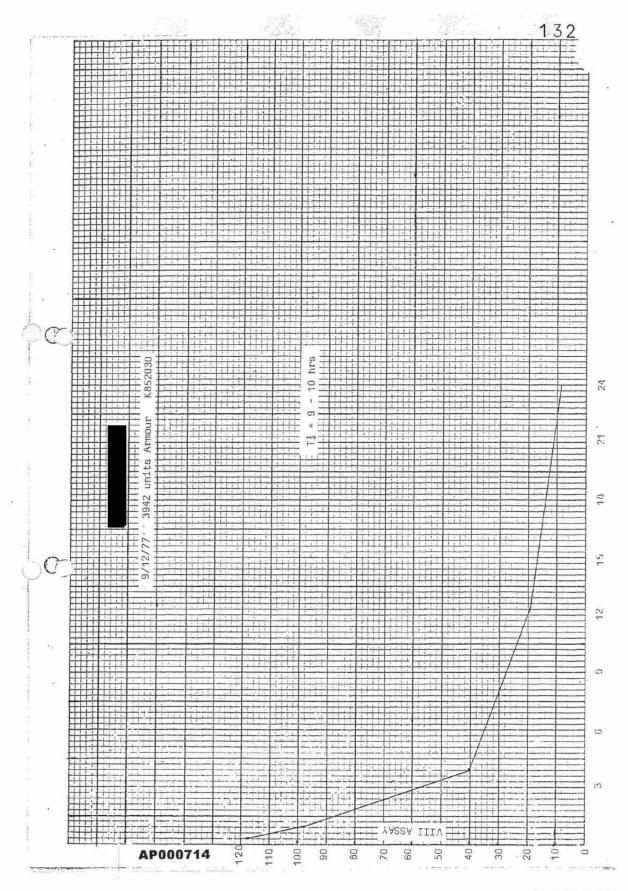
Enclosures

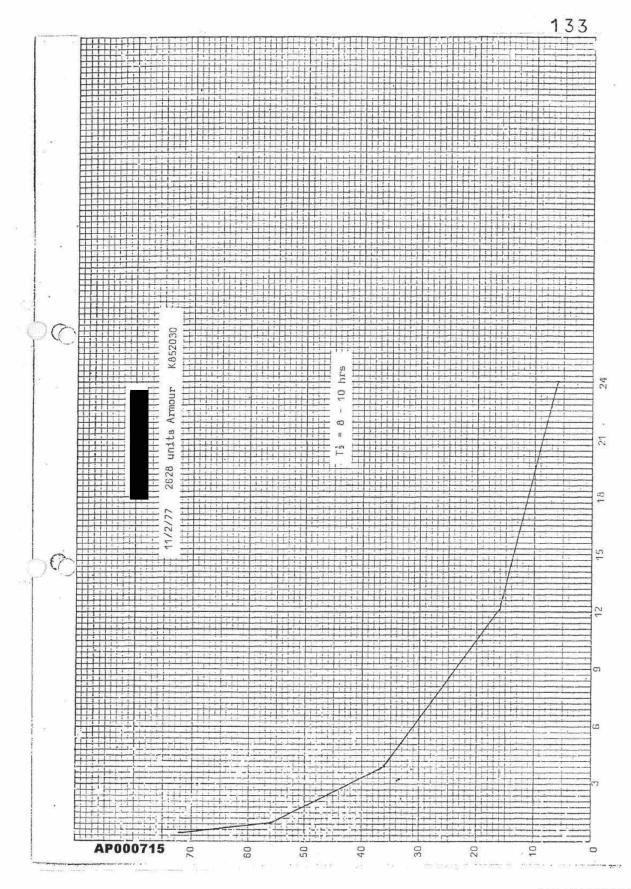
A Major Alliliate of the University of Massachusetts Medical School

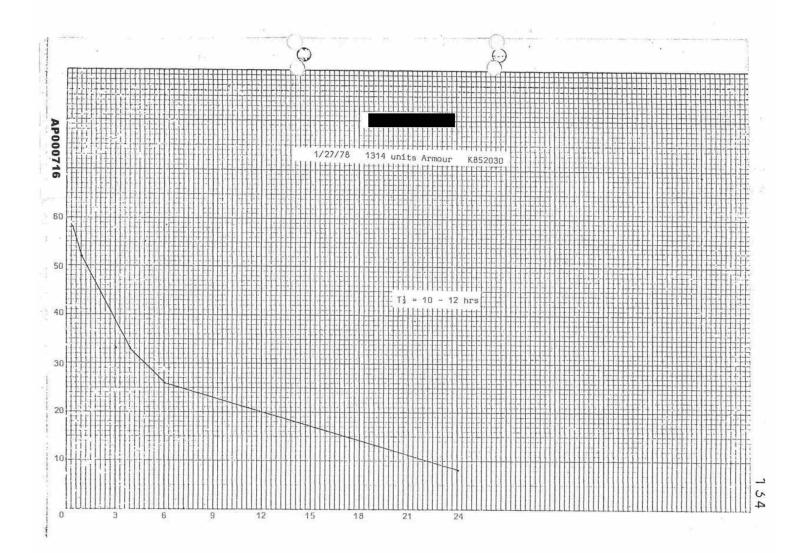
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PART V CLINICAL TRIALS

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1.1. Summary of Clinical Evaluation of AL-1259 - High Potency Factorate -Protocol 101

1.1.1. Introduction

Human blood contains factors which interact to produce blood coagulation. Haemorrhagic disorders occur when one or more factors are absent or decreased. Factor VIII is a plasma protein whose congenital deficiency results in the bleeding disorder known as Haemophilia A.

Factor VIII deficiencies may be corrected with fresh normal plasma, crude concentrates such as cryoprecipitate, antihaemophilic globulin (Cohn Fraction I), or highly purified and concentrated preparations of Factor VIII. Factor VIII concentrates are required to avert over-loading of the circulatory system when a large amount of Factor VIII is required for control of haemorrhage as in surgery or trauma. With clinical usage in these situations requiring Factor VIII in unit amounts of thousands or tens of thousands, a more concentrated and highly purified form of Factor VIII is required. A change in method of manufacture has enabled AL-1259 to meet these criteria. This product will have more AHF units per volume and have less protein. It is a concentrate of Factor VIII made by a modification of the Cohn Fractionation process, yielding not less than 30 units of AHF per ml. The AHF specific activity is approximately 1.0 AHF unit/mg total protein. The solution time will be not more than 30 minutes and will generally reconstitute within 10 minutes. Isoagglutinin titres will be assayed for each lot. AL-1259 is produced from Source Plasma (Human) that has been tested and found negative for HbsAg using a Third Generation test. The final product is similarly tested and found negative for HbsAg. Heparin content is not more than 30 units/30 ml of reconstituted vial.

1.1.2. Objective

This study is designed to demonstrate the safety and efficacy of AL-1259 in treating those patients requiring large amounts of Factor VIII as preparation of elective surgery or to control severe haemorrhage resulting from surgery or trauma.

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1.1.3. Materials and Methods

(a) Selection of Patients

i) Criteria for Inclusion

Patients previously diagnosed as deficient in Antihaemophilic Factor (AHF - Factor VIII) and in need of large prophylactic and therapeutic replacement of Factor VIII are suitable candidates for this study. The subjects will be presented with the objectives of the study, have the possible hazards explained and, if willing to participate in the study, sign informed consent forms.

ii) Criteria for Exclusion

Subjects with known inhibitors of Factor VIII

Any other disease likely to interfere with evaluation of or to prevent completion of the study.

iii) Concurrent Medication

Administration of other types of Antihaemophilic Factor during the course of this study is to be avoided, if possible.

All concurrent medications used during the study will be listed on the case report forms.

- (b) Supplies and Dosage
 - i) AL-1259 represents an AHF concentrate in the high range of potency. It is intended only for intravenous infusion and will be supplied in 50 ml vials of not less than 900 units of AHF to be reconstituted with 30 ml of sterile water for injection. AL-1259 and diluent are to be stored at refrigerator temperature (2°C - 8°C). Freezing may damage the container for the diluent.
 - ii) The determination of dosage will be based on the amount of AL-1259 required to reach desired levels of AHF based on the weight of the patient as calculated by the formula:

Weight in Pounds x AHF Activity desired =

Number of units of AHF needed

AP000718

1.1.4. Procedures and Evaluation

1.1.4.1. Plan of Study

- i) A brief medical history and physical examination will be performed shortly before and at the conclusion of the study. Appropriate information will be recorded on the case report form.
- ii) Laboratory Studies
 - a. Laboratory studies to be performed include:

Factor VIII (%) Pre-infusion the post-infusion

Factor VIII (Half-Life) - on select cases only Single dose infusion

Haemoglobin Pre-infusion

Haematocrit Pre-infusion

HbsAg - Antigen, Antibody Pre-infusion

Bilirubin Pre-infusion

S.G.O.T. Pre-infusion

- iii) Observations During Infusion
 - a. Following each intravenous infusion of AL-1259 careful observation will be made with notation of any local or systemic reactions. All symptoms will be recorded and evaluated for relationship to the injection. A reaction which, in the judgment of the investigator, endangers the volunteer or shows failure of appropriate response to AL-1259 will be grounds for discontinuing further injections in that volunteer. Appropriate therapeutic measures and follow-up will be instituted. Reactions severe enough to cause discontinuation of the study should be reported to Armour Pharmaceutical Company as soon as possible.

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- 1.1.4.2. Evaluation of AL-1259 will be based on the following:
 - Ability to promote effective haemostasis, when applicable. It is well known that an achieved increase in Factor VIII gives haemostasis.
 - ii) Ability to reach calculated levels of Factor VIII.
 - iii) Ability to maintain predicted levels (half-life) of Factor VIII.
 - iv) Incidence and severity of adverse reactions.

1.1.4.3. Recording of Results

- The sponsor will provide report forms on which all laboratory results and clinical evaluations will be recorded for each volunteer.
- As each subject completes the study, the investigator will promptly submit the typewritten case report to:

Karl B. Hansen M.D., Armour Pharmaceutical Company, Greyhound Tower, Phoenix, Arizona 85077.

iii) Federal law requires that following completion of a clinical study a copy of all records of that study is maintained by the Clinical Investigator for a minimum of two years. If requested, the sponsor will, upon receipt of individual case report forms, provide each investigator with a copy of such records for his files.

1.1.5. Unused Medication

1.1.5.1. In accordance with federal law, all unused medications must be accounted for and returned to the sponsor at the conclusion of the study.

> Clinical evaluation of three lots of AL-1259 for safety, potency and efficacy was carried out by the following investigators at four institutions:

STUDY 1 - Harold R. Roberts, M.D. and Philip M. Blatt, M.D., North Carolina Memorial Hospital, University of North Carolina, Chapel Hill, North Carolina 27514 Lot No. K852031

STUDY 2 - Louis M. Aledort, M.D., Mount Sinai School of Medicine, New York, New York 10029, Lot No. K852032

AP000720

STUDY 3 - Margaret W. Hilgartner, M.D., The New York Hospital, Cornell Medical Center, New York, New York 10021, Lot No. K852032

STUDY 4 - Peter H. Levine, M.D., The Memorial Hospital, Worcester, Massachusetts 01605, Lot No. K852030

Each investigator accepted Protocol No. 101 as the guide for his study and completed a case report for each patient.

1.2. Summary of Trials Reported

The following information summarises the four separate evaluations of High Potency Factorate (AL-1259):-

1.2.1. Number of Trials

Four.

1.2.2. Number of Patients Entering Trials

Twenty-eight.

1.2.3. Number Receiving Test Medication and Number Withdrawn

Twenty-eight (none withdrawn).

1.2.4. Daily Dosage Expressed as Mean

Infusion from 1,218 to 5,000 AHF units.

1.2.5. Duration of Dosage

Single infusions.

1.2.6. Summary Results in Terms of Efficacy and Other Statistics - (see attached Table)

Investigators who have wide experience with blood products made no comments when the levels of Factor VIII were less than expected. The ability to reach calculated levels was noted by three quarters of the investigators. No allergic reactions reported. Previous allergic effects seen with cryoprecipitate in 6 patients (Dr. Roberts) and 1 patient (Dr. Aledort).

1.2.7. Adverse Reactions

In one case only was an adverse reaction reported. In this patient the following events took place and was thought by the clinician to be a case of 'short incubation' (non-A, non-B) hepatitis.

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2nd Aug 12th Aug 14th Aug 16th Aug	gust, gust,	1977 1977	- Ma. - Dai - Nai	laise rk uri	and (ine and v(ohills	s ng, id			
Total Bi SGOT SGPT HBsAg	••	•••	•••	1.			2		•••	6.0 1855 2002
HBsAg Negative										
Total Bi SGOT SGPT	llirut 			 						6.0 42 47

1.2.8. Conclusions

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In general, all investigators found the product to be safe, potent and efficacious and no adverse reactions were observed except for the one possibly related case of hepatitis.

It is of especial interest that no allergic reactions occurred in view of the history of allergic reactions to cryoprecipitate in 7/28 patients.

The levels of Factor VIII achieved were higher than calculated in all studies with the exception of Study 3 (Dr. Hilgartner).

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OVERALL RESULTS OF STUDY

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Evaluation By	No. of Patients Entering	No. Receiving Test Medication	No. Withdrawn	Dosage (Range)	Adverse Effects	Efficacy And Other Statistics	Batch Used
Dr. H.R. Roberts and Dr. P.M. Blatt	10	10	None	2250 - 5000 AHF units	1 case (RB) with Hepatitis 10 days after infusion	The one adverse effect cannot necessarily be attributed to AL-1259. AHF values obtained in vivo were 10 - 50% more than expected.	K852031
Dr. L.M. Aledort	8	8	None	1218 - 4872 AHF units	None	AHF values obtained in vivo approximately 30% more than expected values	K852032
Dr. M.W. Hilgartner	5 (3 children) (2 adults)	5	None	1218 - 2436 AHF units	None	AHF values obtained in vivo were 83% of expec- ted values. (With exception of patient MC)	K85203
Dr. P.H. Levine	5 (1 child) (4 adults)	5	None	1214 - 3942 AHF units	None	AHF values obtained in vivo were approximately 16% more than expected values.	K85203

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1.3. <u>STUDY 1</u> - Evaulation of AL-1259 by Drs. H. R. Roberts and P. M. Blatt

Drs. Roberts and Blatt studied ten adult patients with the established diagnosis of Haemophilia A. One patient was treated for a joint haemorrhage and the other nine received prophylactic treatment. Recovery of AHF activity <u>in-vivo</u> averaged 133% of the calculated value. One patient (RB) developed hepatitis (HBsAg negative) ten days after the infusion of AL-1259. He made a prompt and complete recovery and showed no evidence of liver damage on follow-up one month later. In view of the facts that this patient had received 30 bags of cryoprecipitate during the previous three months and that his hepatitis followed the infusion of AL-1259 after an interval shorter than the usually accepted inclubation period for post-transfusion hepatitis, this case of hepatitis is not necessarily to be attributed to AL-1259 but is reported for information. No other adverse effects were observed in any of the ten patients. Results are tabulated overleaf.

Clinical Abstract Patient

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Six bags of cryoprecipitate on each of the following dates: 29th May, 1977, 32st May 1977, 1st June, 1977, 26th June, 1977 and 5th July, 1977.

On	2nd	August,	1977	- infusion of AL-1259
On	12th	August,	1977	- malaise and chills
On	14th	August,	1977	- dark urine
		August,		 nausea, vomiting, icterus, following laboratory values: Bilirubin total 6.0, direct 2.9, SGOT 1855, SGPT 2002 HBsAg negative
On	14th	Septembe	er, 1977	- Clinically entirely well, laboratory values: bilirubin total 6.0, direct 0.2, SGOT 42, SGPT 47.

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Patient	Age	Wt. Kg.	Treatment	Dose* Units	Calculated Rise % AHF	Actual Rise % AHF	Adverse Effects
-	19	57	Joint Haemorrhage	2438	98	128	None
. S . 1 . **	29	54.4	Prophylactic	2250	94	132	None
: -	32	78.3	Prophylactic	3187	90	130	None
142	38	100	Prophylactic	5000	100	134	None
	37	. 90	Prophylactic	4500	100	• 130	None
	32	68	Prophylactic	3750	125	173	None
	25	95	Prophylactic	4400	105	142	None
	21	55	Prophylactic	2250	100	150	· Hepatitis
	28	83	Prophylactic	3957	107 .	121	None
	21	82	Prophylactic	4375	105	117	None

STUDY 1 - HAROLD R. ROBERTS. M.D. AND PHILIP M. BLATT, M.D. TABULATED RESULTS

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	ANTIHE	EMOPHILIC FAC Protocol No.			144
Patient Identificat	ion			St	udy No. 1
Age_ 19 (yrs) Weig	ht(kg)	or 125 (10)	3) Height 71 (1	in) C	ase No. 1
	12 - 6	MEDICAL HIS	STORY	14 1 1	
Kidney Disease [X No 🗌 Yes	Hepatitis	No [X Yes I	Date / ?/
Hypertension	X No Yes	Jaundice	X No [Yes [Date / /
Uremia [X No 🗌 Yes	HAA Test	X Negative [] Positive [Date 10/10/76
•	REACTION	IS FROM PREVI	OUS THERAPY?		
No No		X Yes;	please specify t	herapy and re	eaction:
Itching, hives, e	tc., associa	ted with cry	voprecipitate .		
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			state in the second		
	PH	YSICAL EXAMI	NATION	dilla.	10- i
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L. big toe, left	knee, left h	ip	and the second	- 1998 (fr	delak .
- <u>-</u>					
2		DIAGNOSI	s .		
Prophylaxis	X Join	t Hemorrhage	Muscle H	emorrhage	
Overt Bleeding	*	ive Wound	Surgery		
	CON	COMITANT MED	物政治已经的政治规范	y)	
		ROUTE	SCHEDULE	DATE	DATE
DRUG	SINGLE DOSE	(IM, IV, PO)		1 Struces	signa ia
DRUG					alere in Alexandria
			AP000726		

ſ	Date	Hemoglobin	Hematoc	rit	HAA	Bilir	ubin	S.G.D.T.	
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			Date		в,Р.		alast as		AHF
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	15 minutes Immediate	s Post Infusion							1.28
	1 hr	u . n	11						1.07
	3 hr	n n .							.84
	6 hr	n n		し変					.79
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	No adve		AI DATE AN OF DI	D TIME	EFFECT	cts as i DURATIO	Eliger Section	t-alffelding Al anna an a'	VERITY*
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c	*Classify : linical Resp (the same)						treatm	ent witho	ut chan;
	and the second s				·				
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		MOPHILIC FAC Protocol No.	CONTRACT LIGHT DESCRIPTION ACCOUNTS		146
Patient Identificat	tion				Study No. 1
Age 29 (yrs) Weig		or 120 (1bs) Height 64	(in)	Case No. 2
		MEDICAL HIS		- 	
Kidney Disease [X) No 🗌 Yes	Hepatitis	X No	Yes	Date
Hypertension	X No 🗌 Yes	Jaundice	X No	Yes	Date
Uremia	X No 🗌 Yes	HAA Test	X Negative	Positive	e Date <u>1/10/</u>
2 2	REACTION	S FROM PREVIO	DUS THERAPY?		
X No	e s ^{teñ} r e	Yes; j	please specify	therapy and	l reaction:
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*	181	DIAGNOSIS			
X Prophylaxis	Joint	Hemorrhage		Hemorrhage	
X Prophylaxis					
Overt Bleeding	Massi CONC	Hemorrhage ve Wound OMITANT MEDI	Muscle	y	
Overt Bleeding	Massi CONC	Hemorrhage ve Wound OMITANT MEDI	Muscle	y udy)	
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Immediate Post Infusion 8:45 1.32 1 hr " 9:45 1.03	Date	Hemoglobin	Hemator	prit	HAA	Biliru	ubin.	.S.G.D.T.	14
Lot No. K852031 Dosage 2250 AHF units in60 ml AHF units/vial1164 Solution Time 120 (minutes) Infusion Time 15 (minutes) Calculated AHF Rise 94 & Actual AHF Rise 132 * Date Time B.P. Pulse Temp. PTT AHF% Preinfusion 8/1 8:30 110/70 82 .01 1.32 15 minutes Infusion 8:45 1.32 1.32 1 hr " 9:45 1.03 1.32 3 hr " 11:45 9 hr "	8/.1/.7.7	14.2 (1/77)	43.0 (1	/77.)	(* tri			Normal	
Preinfusion 8/1 8:30 110/70 82 .01 15 minutes Immediate Post Infusion 8:45 1.32 1 hr " 9:45 1.03 3 hr " 11:45 6 hr " 2:45 9 hr " 5:45 12 hr " 8:45 ADVERSE EFFECT SYMPTOMS OF SIGNS DATE AND TIME OF ONSET DURATION SEVERITY*	AHF units/vi	lal <u>1164</u> S	osage <u>22</u> olution T Rise <u>94</u>	50 ime <u>12(</u> %	AHF unit	s in <u>6</u> es) Infu AHF Rise	sion T . <u>132</u>	ime <u>15</u> _%	
15 minutes Immediate Post Infusion 8:45 1.32 1 hr " 9:45 1.03 3 hr " 11:45 .90 6 hr " 2:45 .80 9 hr " 5:45 .80 9 hr " 8:45 .35 ADVERSE EFFECT	Preinfusio	n	-1	T	1	T			·
3 hr " " 11:45 .90 6 hr " " 2:45 .80 9 hr " " 5:45 .80 12 hr " 8:45 .35 ADVERSE EFFECT [X] No adverse effects DATE AND TIME OF ONSET DURATION SYMPTOMS OF SIGNS DATE AND TIME OF ONSET DURATION			n	8:45					1.32
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	4		Protocol No.			148
	Patient Identificati	ion	· · ·			Study No. 1
*	Age <u>32</u> (yrs) Weigh	nt 78.3 (kg)	or 177 (2bs.) Height 75	(in)	Case No. 3
	*, 2 ₁ ,	4 P	MEDICAL HIS	rory .		ge Se Co
	Kidney Disease 🛛] No 🗌 Yes	Hepatitis	X No	Yes	Date
	Hypertension X	No Yes	Jaundice	X No	Yes	Date
	Uremia X	No Yes	HAA Test	X Negative	Positive	Date 8/4/77
		REACTIONS	S FROM PREVIO	US THERAPY?		
	No .		X Yes; p	lease specify	, therapy and	reaction:
	Itching and hives	with cryopre	ecipitate and	i fresh frozer	n plasma.	
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	X Prophylaxis	[] Joint	Hemorrhage	Muscle	Hemorrhage	
*	Overt Bleeding	Massi	ve Wound	Surger	у	
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	DRUG	SINGLE DOSE	ROUTE (IM, IV, PO)	SCHEDULE	DATE STARTI	States and the second sec
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	Patient Identificat	ion	•		Stu	idy No. 1
	Age ³⁸ (yrs) Weig	ht 100 (kg)	or 217 (lbs) Height 72 (in	n) Ca	ise No. 4
	±.		MEDICAL HIS	TORY		6 1 N
	Kidney Disease [X) No 🗌 Yes	Hepatitis	X No]Yes D	ate
	Hypertension [X No 🗌 Yes	Jaundice	X No]Yes D	ate
	Uremia [X) No 🗌 Yes	HAA Test	X Negative] Positive D	ate 8/4/77
		REACTION	S FROM PREVI	OUS THERAPY?		
	No No		X Yes;	please specify th	herapy and re	action:
	Itching associate	d with whole	blood trans	fusion		
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۴		e 1	DIAGNOSIS	3		den inde
	X Prophylaxis	[] Joint	Hemorrhage	12-1-21、12-14日の第日1	morrhage	
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	(Ir		OMITANT MEDI Ilment or be	CATIONS egun during study)	
	DRUG	SINGLE	ROUTE (IM, IV, PO)	SCHEDULE	DATE STARTED	DATE STOPPED
		(現) 18-1	JA MAT			
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AL Lot No. <u>K85031</u> Dosage AHF units/vial <u>1164</u> Solutio Calculated AHF Rise	on Time % ate Time	_ AHF unit	s in es) Infu AHF Rise	134 n sion Tin	me <u>15</u>	(minutes AHF% .01 1.34 1.06 .93
Lot No. <u>K85031</u> Dosage AHF units/vial <u>1164</u> Solution Calculated AHF Rise Da Preinfusion 8/ 15 minutes Immediate Post Infusion 1 hr " " 3 hr " " 6 hr " "	5000 on Time	AHF unit (minut Actual B.P.	s in ces) Infu AHF Rise Pulse	sion Tin 134	me <u>15</u>	AHF% 01 1.34 1.06
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	3.		MOPHILIC FAC Protocol No.		1.034	152 .
	Patient Identifica	tion .		a .	S	tudy No. 1
1	Age 37 (yrs) Wei	ght 90 (kg)	or ¹⁹⁴ (lbs,) Height 68	(in)	Case No. 5.
	4 64 - 10		MEDICAL HIS	TORY		
÷	Kidney Disease (X No Yes	Hepatitis	No No	X Yes	Date 1/5/77
	· Hypertension [X No 🗌 Yes	Jaundice	X No	Yes	Date
·* .	Uremia [X) No 🗌 Yes	HAA Test	X Negative	Positive	Date <u>8/4/77</u>
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	X No		Yes; g	lease specify	therapy and i	reaction:
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		PHY	SICAL EXAMIN	ATION		
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	X Prophylaxis	[] Joint	Hemorrhage	Muscle	Hemorrhage .	
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			OMITANT MEDI Ilment or be	CATIONS gun during stu	dy) ,	
2 3 2 5 3 10 10 81	DRUG	SINGLE DOSE	ROUTE (IM, IV, PO)	SCHEDULE	DATE	DATE STOPPED
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8/4/77 16.7 50.0 Neg. .5 79.0 AL-1259 ADMINISTRATION Lot NoK852031 Dosege 4500 AHF units in 110 ml AHF units in 110 ml AHF units/vial_1164 Solution Time 60 (minutes) Infusion Time 15 (minute) Calculated AHF Rise 100 % Actual AHF Rise 130 % Date Time B.P. Pulse Temp. PTT AHF Preinfusion 8/4 145/80 78 .0 15 minutes Immediate Post Infusion 1.3 1.3 1 hr " .10 8 hr " 9 hr "					· · · · · · · · · · · · · · · · · · ·		
AL-1259 ADMINISTRATION Lot No. K852031 Dosage 4500 AHF units in 110 ml AHF units/vial_1184 Solution Time 60 (minutes) Infusion Time 15 (minute) Calculated AHF Rise 100 % Actual AHF Rise 130 % Date Time B.P. Pulse Temp. PTT AHF Preinfusion 8/4 145/80 78 .cc .cc 15 minutes Immediate Post Infusion 1.3 1.3 .cc .cc 3 hr " .cc .cc .cc .cc .cc 3 hr " .cc .cc .cc .cc .cc 1 hr " .cc .cc .cc .cc .cc 1 hr " .cc .cc .cc .cc .cc 3 hr " .cc .cc .cc .cc .cc 3 hr " .cc .cc .cc .cc .cc 1 hr " .cc .cc .cc<	Date	Hemoglobin	Hematocrit	: HAA	Bilirubi	.n S.G.D.T.	15
Lot No. K852031 Dosage 4500 AHF units in 110 ml AHF units/vial 1184 Solution Time 60 (minutes) Infusion Time 15 (minutes) Calculated AHF Rise 100 % Actual AHF Rise 130 % Date Time B.P. Pulse Temp. PTT AHF Preinfusion 8/4 145/80 78 15 minutes Infusion 8/4 145/80 78 1 hr " " 3. hr " " 3. hr " <t< td=""><td>····8/4/77····</td><td>16.7</td><td>50.0</td><td>Neg.</td><td>.5</td><td>79.0</td><td></td></t<>	····8/4/77····	16.7	50.0	Neg.	.5	79.0	
15 minutes Immediate Post Infusion 1.3 1 hr " 1 hr " 3 hr " 6 hr " 9 hr " 12 hr " Adverse effects Adverse effects as in table: SYMPTOMS OF SIGNS DATE AND TIME OF ONSET DURATION	HF units/v:	ial <u>1164</u> S	osage 4500 olution Time Rise 100	AHF unit	ts in <u>110</u> tes) Infusio AHF Rise <u>1</u>	on Time <u>15</u> <u>30 </u> %	(minut
Immediate Post Infusion 1 1 hr " 1.0 3 hr " 1.0 3 hr "	Preinfusio	חכ	8/4	. 145/80	. 78		.0
3. hr "			1				1.3
6 hr " .9 6 hr " .8 9 hr " .8 9 hr " .7 12 hr " .3 ADVERSE EFFECT X No adverse effects Image: Adverse effects as in table: SYMPTOMS OF SIGNS DATE AND TIME OF ONSET DURATION SEVERITY*	1 hr	10 , N		一個相違			1.0
9 hr " " .7 12 hr " " .3 ADVERSE EFFECT X No adverse effects SYMPTOMS OF SIGNS DATE AND TIME OF ONSET DURATION SEVERITY*	.3. hr	n n .					.9(
12 hr " .7 12 hr " .3 ADVERSE EFFECT .3 Image: Symptoms of signs DATE AND TIME OF ONSET DURATION SEVERITY*	6 hr	n n	14 (4)	1445			.83
ADVERSE EFFECT	9 hr			4 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1.			.7
No adverse effects Adverse effects as in table: SYMPTOMS OF SIGNS DATE AND TIME OF ONSET DURATION	12 hr	n n					.3
		OF SIGNS	DATE AND T OF ONSE	Adverse effe			ERITY*
	The second		and Castleria	an Anitestation .	Automation - The	Maker or Manual -	L. SALLEL
AP000735					۸D	000735	

	Patient Identifica	8. I.S.	MOPHILIC FAC Protocol No.			154 Study No. <u>1</u>
	Age <u>32</u> (yrs) Wei	ght(<i>kg</i>)	or 150 (7bs.		(in)	Case No. 6
			MEDICAL HIS	TORY		
	Kidney Disease	X No Yes	Hepatitis	X No	Yes	Date 8/3/77
	Hypertension	X No 🗌 Yes	Jaundice	X No	Yes	Date 8/3/77
	Uremia	X No Yes	HAA Test	X Negative	Positive	Date <u>8/3/77</u>
	4 4 (8)	REACTIONS	FROM PREVIO	DUS THERAPY?	1944-525.	
÷	No No		X Yes; g	please specify	therapy and	reaction:
r	Itching and hives	s from cryopre	cipitate and	plasma		
().	· ·			Although Children		
2 m V		د محمد مربع میلو دانود				
	-		'나 안 생활한다 			
ан — — — — — — — — — — — — — — — — — — —		PHY	SICAL EXAMIN	ATION		
	<u>Number</u> and list e treatment examina Use additional nu	tion, use sam	e number and	indicate any	changes in e	On post- each finding.
	Pre-	Treatment			Post-Treatmer	it .
		a a second		40 Statil#3.		
53			$= \frac{E_{\rm pol}}{2^{\rm pol}}$	Se de		A. A. I
0.	inter a	i sai m			and Mer	
5 m ⁴¹		* }	DIAGNOSIS			
	X Prophylaxis	🛄 Joint	Hemorrhage	Muscle	Hemorrhage	
	Overt Bleeding	Massiv	ve Wound	Surgery	,	
	(1	CONCO n use at enrol	DMITANT MEDI llment or be		uđy)	
	DRUG	SINGLE DOSE	ROUTE (IM, IV, PO)	SCHEDULE	DATE STARTI	
i int	None	7 4	4.4		望。魏	
Pr 1						
and the	All Car all	alater atter	allen allen.	AP000736	ality Ality	in the second

ſ	Date	Hemoglobin	Hematoc	rit	HAA	Bilir	ubin	S.G.D.T.	155
-	8/3/77	17.8	. 54.0		Neg.			66	1.00
	HF units/v	52031 [ial	Dosage <u>3</u> Solution T	750 ime 90)(minut	s in es) İnfu	sion 1	Fime <u>15</u>	_(minutes)
		alculated VI	Date	B	B.P.		11111250	State of the	AHF%
-	Preinfusio	חס	8/3		128/80	75			<.01 u/m
	15 minute: Immediate	s Post Infusic	"						1.73
	1 hr	10 . H							1.48
	3 hr	13 17	μ						1.13
	6 hr	n n	- n	小僧					1.01
	9 hr	n , " "	n						.95
	12 hr	n n	4					5 2. m	.57
	X No adve	erse effects	, Marcal Me	Adv	EFFECT erse effe		ante. Rectorera	Net 1986. /	VERITY*
	inical Res	reaction as1 ponse <u>The</u> al response c	patient w	as not	bleeding		infus	ion, ther	efore,
			des di	-			1	AP00073	-

3		Protocol No.	UR (HUMAN) 101	10 C	156
Patient Identificati	on	-		St	udy Nc. 1
Age_25_(yrs) Weigh	nt(kg)	or 208 (1bs.	Height 73	(in) C	Case No. 7
n 1		MEDICAL HIST	ORY	12 : chi (13 : chi) 2 : chi (13 : chi)	1. C
Kidney Disease 🗋	No 🗌 Yes	Hepatitis	X No	Yes	Date <u>8/3/77</u>
Hypertension	No 🗌 Yes	Jaundice	X No	🗋 Yes	Date 8/3/77
Uremia 🔯	No 🗌 Yes	HAA Test	X Negative	Positive	Date 8/3/77
	REACTION	S FROM PREVIO	US THERAPY?		
X No		Yes; p	lease specify	therapy and r	eaction:
4	, i			國憲 憲法	
	<u>`</u>	- 医前胃		的复数 建煤	S. 19-2
		有深. 劉翊		建建 法法	
	PHY	SICAL EXAMIN	ATION	财物的信	Will Bell
Number and list ea treatment examinat Use additional num Pre-T:	ion, use san	ne number and	indicate any itive findings	changes in ea	ch finding
			n an		
1		Sec. Barrier	en e		and and an
			and the second		
2 W				的制度的问题。	
	1 1948 1948 	DIAGNOSIS			
X Prophylaxis	Joint	DIAGNOSIS Hemorrhage		Hemorrhage	
X Prophylaxis		Reality and	Muscle		
Overt Bleeding	Massi CONC	Hemorrhage ve Wound OMITANT MEDI	Muscle		
Overt Bleeding	Massi CONC	Hemorrhage ve Wound OMITANT MEDI	Muscle		DATE
Overt Bleeding (In	CONC use at enro	Hemorrhage ve Wound OMITANT MEDI <i>liment or be</i> ROUTE (<i>IM</i> , <i>IV</i> ,	Muscle Surgery CATIONS gun during stu	dy)	
Overt Bleeding (In DRUG	CONC use at enro	Hemorrhage ve Wound OMITANT MEDI <i>liment or be</i> ROUTE (<i>IM</i> , <i>IV</i> ,	Muscle Surgery CATIONS gun during stu	dy)	
Dvert Bleeding (In DRUG	Massi CONC use at enro SINGLE DOSE	Hemorrhage ve Wound OMITANT MEDI <i>liment or be</i> ROUTE (<i>IM</i> , <i>IV</i> ,	Muscle Surgery CATIONS gun during stu	dy)	

					·	
8/3/77	17.5	50.0	Neg.	1.0	144	1.00
Date	Hemoglobin	Hematocrit	HAA	Bilirubin	S.G.O.T.	157

AL-1259 ADMINISTRATION

Lot No. K852031 Dosage 4400 AHF units in 120 ml

AF units/vial 1164 Solution Time 60 (minutes) Infusion Time 15 (minutes)

Calculated AHF Rise 105 % Actual AHF Rise 142 %

	Date	Time	B.P.	Pulse	Temp.	PTT	AHF%
Preinfusion	8/3		135/85	78		98-29 4 - 19	<.01
15 minutes Immediate Post Infusion				•			1.42
1 hr " "	1	-416				1	1.20
3 hr " "				源。			1.03
6 hr " "						190 - 14 1	.92
9 hr ""	1			Step.		2	.83
12 hr " "						말신	.51

ADVERSE EFFECT

X No adverse effects Adverse effects as in table:

SYMPTOMS OF SIGNS DATE AND TIME DURATION SEVERITY*

*Classify reaction as 1 = mild; 2 = moderate; 3 = severe

Clinical Pesponse ____ The patient was not bleeding prior to infusion, therefore,

clinical response could not be evaluated.

AP000739

, M.D. Date 9/13/77

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Signature of Investigator

Hypertension X No Yes Jaundice X No Yes Date_0/2/ Uremia X No Yes HAA Test X Negative Positive Date_0/2/ REACTIONS FROM PREVIOUS THERAPY? Image: Constraint of the constraint	ar j ^r s ^r		HILIC FACT tocol No.	FOR (HUMAN) 101		158
Age 21 (gre) Weight (kg) or 118 (lbs) Height 71 (fn) Case No	Patient Identification	n				Study No. 1
MEDICAL HISTORY Kidney Disease X No Yes Hepetitis X No Yes Date B/2/ Hypertension X No Yes Jaundie X No Yes Date B/2/ Uremia X No Yes HA Test X Negative Positive Date B/2/ REACTIONS FROM FREVIOUS THERAPY?	Age 21 (yrs) Weight	(kg) or	118 (Zbs)	Height 71	(in)	1. 1. 1.
Hypertension X No Yes Jaundice X No Yes Data 0/2/ Uremia X No Yes HAA Test X Negative Positive Data 0/2/ REACTIONS FROM PREVIOUS THERAPY? Image: Constraint of the			DICAL HIST	ORY		
Uremia No Yes HAA Test Negative Positive Data <u>0/2/</u> REACTIONS FROM <u>PREVIOUS</u> THERAPY? No Yes; please specify therapy and reaction: PHYSICAL EXAMINATION Number and list each positive finding in pre-treatment examination. On post- treatment examination, use same number and indicate any <u>changes</u> in each findings Use additional numbers to list any new positive findings. Pre-Treatment Post-Treatment Pre-Treatment Post-Treatment DIAGNOSIS Prophylexis Joint Hemorrhage Muscle Hemorrhage Overt Bleeding Massive Wound Surgery CONCOMITANT MEDICATIONS (In use at envolument or begun during study) DRUG SINCLE ROUTE DOSE (IM, TV, SCHEDULE DATE STARTED STOPPED None ADDING AP000740	Kidney Disease 🗶 M	No Yes	Hepatitis	X No	Yes	Date <u>8/2/77</u>
REACTIONS FROM <u>FREVIOUS</u> THERAPY? Image: State in the sta	Hypertension X	Vo 🗌 Yes .	Jaundice	X No	Yes .	Date_ 8/2/77
No Yes; please specify therapy and reaction: PHYSICAL EXAMINATION Number and list each positive finding in pre-treatment examination. On post-treatment examination, use some number and inlicate any okanges in each finding Use additional numbers to list any new positive findings. Pre-Treatment Post-Treatment Pre-Treatment Post-Treatment OIAGNOSIS OIAGNOSIS [] Overt Bleeding Messive Wound Surgery CONCOMITANT MEDICATIONS (In use at enrollment or begun during study) DATE DRUG SINGLE ROUTE / PO) SCHEDULE DATE None	Uremia 🔀 M	io 🗌 Yes I	HAA Test	X Negative	Positive	e Date <u>8/2/77</u>
PHYSICAL EXAMINATION Number and list each positive finding in pre-treatment examination. On post-treatment examination, use same number and indicate any changes in each finding Use additional numbers to list any new positive findings. Pre-Treatment Post-Treatment Pre-Treatment Post-Treatment DIAGNOSIS		REACTIONS F	ROM PREVIO	US THERAPY?		
PHYSICAL EXAMINATION Number and list each positive finding in pre-treatment examination. On post- treatment examination, use same number and indicate any <u>changes</u> in each finding Use additional numbers to list any new positive findings. Pre-Treatment Post-Treatment OIAGNOSIS	X No		Yes; p	lease specify	therapy and	l reaction:
PHYSICAL EXAMINATION Number and list each positive finding in pre-treatment examination. On post- treatment examination, use same number and indicate any <u>changes</u> in each finding Use additional numbers to list any new positive findings. Pre-Treatment Post-Treatment OIAGNOSIS		S - Selfika		Contraction (
Number and list each positive finding in pre-treatment examination. On post-treatment examination, use same number and indicate any changes in each finding Use additional numbers to list any new positive findings. Pre-Treatment Post-Treatment OIAGNOSIS	Sec. 1 are		Service and	la dila ¹⁷ d	Carl Martin	
Number and list each positive finding in pre-treatment examination. On post-treatment examination, use same number and indicate any changes in each finding Use additional numbers to list any new positive findings. Pre-Treatment Post-Treatment OIAGNOSIS		a second second	nor W		art Mager	
Number and list each positive finding in pre-treatment examination. On post-treatment examination, use same number and indicate any changes in each finding Use additional numbers to list any new positive findings. Pre-Treatment Post-Treatment OIAGNOSIS		DUVET			Carl Alter	sille deb.
treatment examination, use same number and indicate any changes in each finding Use additional numbers to list any new positive findings. Pre-Treatment Post-Treatment DIAGNDSIS Image: Stream of the	- 1		ger de per Mada			
DIAGNOSIS DIAGNOSIS DIAGNOSIS DIAGNOSIS DIAGNOSIS DIAGNOSIS DIAGNOSIS Diagenvector and the answer of the an	Use additional numbe	rs to list ar	iunder and iy new pos	itive finding	s.	
Image: Single Drug Image: Single Drug Single Drug Single Drug Single Drug Date Started Date Stopped None Image: Single Drug Image: Single Drug Image: Single Drug Schedule Date Started Date Stopped None Image: Single Drug Image: Single Drug </td <td>116 116</td> <td></td> <td></td> <td></td> <td></td> <td></td>	116 116					
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Image: Single Drug Image: Single Drug Single Drug Single Drug Single Drug Date Started Date Stopped None Image: Single Drug Image: Single Drug Image: Single Drug Schedule Date Started Date Stopped None Image: Single Drug Image: Single Drug </td <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>						
Overt Bleeding Massive Wound Surgery CONCOMITANT MEDICATIONS (In use at enrollment or begun during study) DRUG DRUG SINGLE DOSE ROUTE (IM, IV, PO) SCHEDULE DATE STARTED DATE STOPPED Nons Image: Im	Prophylaxis			和中心的问题。 第二	and the party is storted in	
CONCOMITANT MEDICATIONS (In use at enrollment or begun during study) DRUG SINGLE DOSE ROUTE (IM, IV, PO) SCHEDULE DATE STARTED DATE STOPPED Nons		_				
(In use at enrollment or begun during study) DRUG SINGLE DOSE ROUTE (IM, IV, PO) SCHEDULE DATE STAPPED None						
DRUG SINGLE DOSE (IM, IV, PO) SCHEDULE DATE STARTED DATE STOPPED None - - AP000740 -	(In u				ıdy)	
AP000740	DRUG		IM, IV,	SCHEDULE	TAX SOME CONTRACTOR OF A DATA SOLUTION OF A	
AP000740	None :	ada Sarta	della della	Andreas de	light spine	St. A. Shine
		· • •				
	. 65		Silve 1	AP000740		an Andreas
ACCOUNTS AND ADDRESS AND ADDRESS ADDRES	(99)	1 N 1	- 49-10. A.S.			an an air an

Date	Hemoglobin	Hematoc	rit	HAA	Biliru	ubin	S.G.O.T	. 1!
8/2/77	15.2	46.0) . .	Neg.			30	1.1
						ř.,		1.2
_ot No. <u>K85</u> AHF units/via Cal		sage lution T Rise _100	2250 ime 90	(minut Actual	s in tes) Infu AHF Rise	sion 150	Γime <u>15</u>	(minut
		Date	Time	в.р.	`Pulse	Temp	p. PTT	AHF
Preinfusion	i s	8/2/77	10	122/80	75			<.01
15 minutes Immediate P	ost Infúsion							1.50
1 hr	н							1.20
3 hr	н 5)							• 1.01
6 hr	n U							.92
9 hr	n n	치관			朝 雪			.83
12 hr	11 17			Mart				.45
No advers SYMPTOMS OF Hepatitis		DATE AN OF Of	X Advi D TIME NSET	a sida	DURATION		Same and a second	EVERITY
linical Respo	eaction as1 = onse <u>The pa</u> sponse could	atient wa	as not l	oleeding		infus	ion, the	refore,
an Addition				reger af en der F			ano ana Natari	
			•				AP00074	¥1
and the second have	以為出土的"有效"等的。	and the second second	10000000			1. 292545	P. C. Britson and Company	Statistic (1.5

Patient Identific					
	ation		- 10 - A	S	tudy No. 1_
Age ²⁸ (yrs) We		or 182 (1bs)) Height 67		Case No. 9
Kidney Disease	X No Yes	Hepatitis	No No	X Yes	Date 4//76
Hypertension	X No Yes	Jaundice	X No	Yes	Date
Uremia	X No Yes	HAA Test	X Negative	Positive	Date <u>12/9/76</u>
5	REACTION	S FROM PREVIO	DUS THERAPY?		
No No	1. 1.	X Yes; p	lease specify	therapy and 1	reaction:
Itching and hives	with fresh fro	izen plasma ar	nd cryoprecipi	tate	
5. 5 x 5.2	r fa - n i				
	LA.	动、 流振	and the	ales. Sales S	
	PH	YSTCAL EXAMIN			
					iker lefter
treatment examin	ation, use sa	me number and	indicate any	changes in ea	On post- ch finding.
Pre	-Treatment		reisi ner Allis desp	Post-Treatment	
4	and the second s				Martin Martin
	7	小学がの問題			國南部同時代中華
				iden i lette	an an i
Y Prophylayis		and defined	training - Shines	Homonrhago	
	*				
U overt breeding	and the state of the second	和自己的正式的考虑的	and the state of the		
· · · · · · · · · · · · · · · · · · ·				uđy)	
DRUG	SINGLE DOSE	ROUTE (IM, IV, PO)	SCHEDULE	DATE	DATE STOPPED
None	dina datan	Alter Alter	Sec. Ber	dan shiriya	h an dùin, i
ight wher after	And Strategy	and the states	Service State	Realize Mail State	
			AP000742	2	. Marine Marine
	NUMBER OF STREET, STRE				
	Kidney Disease Hypertension Uremia No Itching and hives <u>Mumber</u> and list treatment examin Use additional m Pre No Pre	Kidney Disease No Yes Hypertension No Yes Uremia X No Yes REACTION No No Yes Itching and hives with fresh fro PH Number and list each positive treatment examination, use sature treatment examination, use sature treatment Pre-Treatment Yrophylaxis Joint Overt Bleeding Massi CONC (In use at enroce the position of the po	MEDICAL HIST Kidney Disease No Yes Hepatitis Hypertension No Yes Jaundice Uremia No Yes HAA Test REACTIONS FROM PREVICE No Yes; p No Yes; p Itohing and hives with fresh frozen plasma and positive finding in p treatment examination, use same number and Use additional numbers to List any new pos Pre-Treatment DIAGNOSIS Y Prophylaxis Joint Hemorrhage Overt Bleeding Massive Wound CONCOMITANT MEDIC (In use at enrollment or be DRUG SINGLE DRUG SINGLE None None	MEDICAL HISTORY Kidney Disease No Yes Hypertension No Yes Uremia No Yes MA Test No Baundice No Uremia No Yes REACTIONS FROM PREVIOUS THERAPY? No No X Yes; please specify Itohing and hives with fresh frozen plasma and cryoprecipt PHYSICAL EXAMINATION Mmber and List each positive finding in pre-treatment treatment examination, use same number and indicate any Use additional numbers to list any new positive finding. Pre-Treatment Image: Pre-Treatment Image: Pre-Treatment Image: Pre-Treatment Image: Prophylaxis Joint Hemorrhage Overt Bleeding CONCOMITANT MEDICATIONS (In use at enrollment or begin during str DRUG SINGLE DDISE (IM, TV, ZO) SCHEDULE None	MEDICAL HISTORY Kidney Disease X No Yes Hypertension No Yes Jaundice No Yes Uremia No Yes REACTIONS FROM PREVIOUS THERAPY? Positive REACTIONS FROM PREVIOUS THERAPY? No Xes, please specify therapy and z Itching and hives with fresh frozen plasma and cryoprecipitate PHYSICAL EXAMINATION Mumber and List each positive finding in pre-treatment examination. The additional numbers to list any new positive findings. Post-Treatment Pre-Treatment Post-Treatment Post-Treatment DIAGNOSIS Joint Hemorrhage Muscle Hemorrhage Overt Eleeding Massive Wound Surgery CONCOMITANT MEDICATIONS CONCOMITANT MEDICATIONS DRUG SINCLE RCUTE DOSE SCHEDULE DATE None

Date	Hemoglobin	Hematocrit		HAA	Biliru	bin	S.G.D.T.	1-61
8/3/77		46.0		Neg.	.5	- 1.	49	۱ <u>.</u>
				. <u>1</u> . 4. 41		<u>y 14</u>	a siça i i	1 - ¹⁰ - 1 - 1
AHF units/vi	52031 Do lal_164 So alculated AHF F	sage <u>3957</u> lution Time Rise <u>107</u>	<u>90</u>	(minuto Actual)	s in <u>10</u> es) Infus AHF Rise	ion T	ime. 15	(minutes AHF%
Preinfusio	'n	8/3		118/76	76			.01
, 15 minutes Immediate	Post Infusion							1.21
1 hr	н р							.99
3 hr	ы п							.86
6 hr	и и		i de					.81
9 hr	n n							.65
12 hr	n î							35
X No adve	rse effects DF SIGNS		Adve	FFECT	DURATION			/ERITY*
Clinical Resp	reaction as1 = ponse <u>The pa</u> response could	atient was	not l	bleeding p	自己的意思	infus	ion, there	fore,
in an	er en	na sena da la sena da Referencia da la sena d			a dalara		AP000743	1

			MOPHILIC FACT Protocol No.			162
÷ 1	Patient Identificat:	Lon	•	garde i de	김 수도 벗어졌다.	Study No. 1
	Age_21 (yrs) Weigh	nt(kg)	or 180 (1bs) MEDICAL HIST	a ten la acces	<u>(</u> in)	Case No. <u>10</u>
	Kidney Disease 🕅	No TYes	Hepatitis	X No	Yes	Date 8/3/77
	Hypertension X		Jaundice		T Yes	Date 8/3/77
) No 🗌 Yes	HAA Test	X Negative	and the second	Theat
un Terra	•	REACTIONS	FROM PREVIC	US THERAPY?		
	No No	n ny paoline ny paol Ny faritr'ora dia mampiasa mandritry ny faritr'ora dia mandritry dia mandritry dia mandritry dia mandritry dia m	X Yes; p	lease specify	therapy and	reaction:
<u></u>	Itching and hives wi	th fresh fro	zen plasma a	nd cryoprecipi	itate	通常、通常、1
().		al an agusta Russian		• Angel - Charles		
	학교가 운영하다 명령	a de palítica	14月1日1月1日	a Children Children		
		- 2 - my	de des	alter alter	Alter Alter	aller dies
		PHY	SICAL EXAMIN	ATION		
	Number and list ea treatment examinat Use additional num	ion, use sam	e number and	indicate any	changes in e	On post- ach finding.
	Pre-T	reatment			Post-Treatmen	ť
2						
r l					ting and	
\geq				All All	Alter Alter	

			DIAGNOSIS			
al .	Prophylaxis	. Joint	filling stalling	. Muscle	Hemorrhage	
	∑ Prophylaxis		Hemorrhage		Hemorrhage V	
	 ☐ Overt Bleeding	Massi CONC	Hemorrhage ve Wound DMITANT MEDIO	Surger	y	
	 ☐ Overt Bleeding	Massi CONC	Hemorrhage ve Wound DMITANT MEDIO	Surger	(udy)	
	Uvert Bleeding	CONCI use at enro	Hemorrhage ve Wound DMITANT MEDIG <i>liment or beg</i> ROUTE (IM, IV,.	Surgery CATIONS gun during stu	ر بطي) DATE	
	Overt Bleeding (In DRUG	CONCI use at enro	Hemorrhage ve Wound DMITANT MEDIG <i>liment or beg</i> ROUTE (IM, IV,.	Surger CATIONS gun during stu	ر بطي) DATE	
	Overt Bleeding (In DRUG	CONCI use at enro	Hemorrhage ve Wound DMITANT MEDIG <i>liment or beg</i> ROUTE (IM, IV,.	Surger CATIONS gun during stu	ر بطي) DATE	

Date	Hemoglobin	Hematocrit	HAA	Bilirubin	S.G.D.T.	163
8/2/77	16.7	48.0	Neg.		47.0	Ś.
				-		1 - 16 <u>1</u> - 184

AL-1259 ADMINISTRATION

Lot No. K852031 Dosage 4375 AHF units in 90 ml

AHF units/vial 1164 Solution Time 60 (minutes) Infusion Time 15 (minutes)

Calculated AHF Rise 105 % Actual AHF Rise 117 %

	Date	Time	B.P.	Pulse	Temp.	PTT	AHF%
Preinfusion	. 8/2		125/84	. 70			<0,1 u/ml
15 minutes Immediate Post Infusion	8/2						1.17 u/ml
1 hr "	8/2		-3:-41				1.00 u/ml
3 hr " "	8/2				新编		.88 u/ml
6 hr " "	8/2						.79
9 hr " "	8/2						.68
12 hr " "	8/2						.39

ADVERSE EFFECT

X No adverse effects

 $\langle \langle$

Adverse effects as in table:

	SYMPTOMS OF SIGNS	DATE AND TIME OF ONSET	DURATION	SEVERITY*
T		- ⁻ - 61	 A. Contact and 	genderiche de co
ŵr 1		in North Proops Andrew A		Par an and the failed and
c -	*Classify reaction as linical Response <u>The</u> clinical response of	철말 같은 가 없는 것을 수 있다.	eding prior to inf	fusion therefore,
12				
	the second second second		de las de de	AP000745
		말랐는 것같아요. 그렇겠는 같이라는 것		
			Date 9/13/77	a series and

ARMOUR000953

43

1.4. STUDY 2 - Evaluation of AL-1259 by Dr. L. M.Aledort

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Dr. Aledort studied eight patients with the established diagnosis of Haemophilia A. Four patients were treated for joint haemorrhages and four were prepared for various surgical procedures. In this study recovery of AHF activity <u>in-vivo</u> was poorer than in the other three studies, averaging 51% of the calculated values. Assay methods for AHF activity are known to vary considerably in different institutions. The investigator, who has a wide experience with AHF products, made no comment that recovery was unsatisfactory; hence it would appear that such recoveries are not unusual in his institution. In study 3, using the same lot of AL-1259 as study 2, much better recovery was observed. No adverse effects were observed in any of the eight patients in study 2. The clinical response was satisfactory in each case. Results are summarized overleaf.

AP000746

ARMOUR000954

ARMO0000092_0168

a English	29	98	Surgery Preparation	- 3654	93	42	None
	27	. 70	Surgery Preparation	2436	88	55	None
	30	97	Surgery Preparation	4872	100	74	None
	49	73	Joint Haemorrhage	2436	. 85 -	34.7	None
	32	52 	Joint Haemorrhage	1218	58	26	None
	24	52	Joint Haemorrhage	1218	58	33.7	None
	30	61	Surgery Preparation	2436	100	44.7	None
	8	34	Joint Haemorrhage	. 1218		31.8	None
		1.161		- dide a			l and a second barrier and a

STUDY 2 - LOUIS ALEDORT, M.D.

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AP000747

TABULATED RESULTS

	Patient Identificat	F	MC-123 MOPHILIC FA	CTOR (HUMAN)	S	166 tudy No. 2
5	Age 29 (yrs) Weig		or (1b	s) Height 5'9"		Case No. 1
			MEDICAL HI	• 9	1.446	
	Kidney Disease 🛛	No Yes	Hepatitis	s 🗶 No	Yes .	Date
	Hypertension	No Yes	Jaundice	X No	Yes	Date
,	Uremia 🛛	No 🗌 Yes	HAA Test	🗙 Negative	D Positive	Date
	Lannes martine y contra diversi	REACTIONS	FROM PREVI	THERAPY?		
	No		X Yes;	please specify	therapy and i	reaction:
C.	Urticaria p Cryop:	recipitate an	d F.F.P. fi	ve years ago d	eveloped palpi	tations
R	and tightness in (chest to Fact	or VIII Cor	ncentrate		
6 ja				and the	da Ak	
		a service a		法国际运动的行动		操制的标志
la la		PHY	SICAL EXAMI	INATION	an in	
	Number and list ed treatment examinat Use additional num	tion, use same	e number an	nd indicate any	changes in ea	On post- ach finding.
	. Pre-1	reatment			Post-Treatment	
	P.E WNL Exc. fo	or flexion com	ntracture	P.E u	nchanged	
1	right knee	2 - 48 ²⁰ ,	5 G.C.			st Alles Al
Y.		e Madal	- Sugar			
			DIAGNOSI	S ·		
	🌅 Prophylaxis	💽 Joint	Hemorrhage	Muscle	Hemorrhage	
lite Transformer and	Overt Bleeding	🗌 Massiv	ve Wound	X Surger	y .	000748
	(In		DMITANT MED llment or b	ICATIONS egun during sta		000748
	DRUG	SINGLE	ROUTE (IM, IV, PO)	SCHEDULE	DATE	DATE STOPPED
	BENADRYL	25 mg	I.V.	Prior to fact transfusion	or . 10/19	10/19
	DALMANE	30.mg	P.O.	QHS PRN	10/11	. Alexand
	CODEINE	30 mg	P.0.	Q3H PRN	10/11	
	TYLENOL	5 gr (2)	P.0.	Q4H PRN	10/11	

10/11/77 14.0 43:3 NEG. AL-1259 ADMINISTRATION Lot No. K852032 Dosage 3654 AHF units AHF units/vial 1218 Solution Time 50 (minus) Calculated AHF Rise 93 % Actual Date Time B.P. Preinfusion	ts in <u>90</u> <i>tes)</i> Infus: AHF Rise	ml ion Time 42 %	40 (minu PTT Al <1%	HF%
AL-1259 ADMINISTRATION Lot No. <u>K852032</u> Dosage <u>3654</u> AHF unital AHF units/vial <u>1218</u> Solution Time <u>50</u> (minus Calculated AHF Rise <u>93</u> % Actual Date Time B.P. Preinfusion Immediate Post Infusion 1 hr " " 4 hr " "	ts in <u>90</u> <i>tes)</i> Infus: AHF Rise	ion Time 42 🐒	PTT AI	HF%
Lot No. <u>K852032</u> Dosage <u>3654</u> AHF unit AHF units/vial <u>1218</u> Solution Time <u>50</u> (minus Calculated AHF Rise <u>93</u> & Actual Date Time B.P. Preinfusion Immediate Post Infusion 1 hr " " 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	ts in <u>90</u> <i>tes)</i> Infus: AHF Rise	ion Time 42 🐒	PTT AI	HF%
AHF units/vial1218_Solution Time50_(minu: Calculated AHF Rise93 % Actual Date Time B.P. Preinfusion	tes) Infus:	ion Time 42 🐒	PTT AI	HF%
Calculated AHF Rise 93 & Actual Date Time B.P. Preinfusion Immediate Post Infusion 1 hr " " 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	AHF Rise	42 %	PTT AI	HF%
Date Time B.P. Preinfusion	alle somer the same	George and States	<1% 41	.8%
Preinfusion Immediate Post Infusion 1 hr 4 hr 12 hr	Pulse	Temp: 1	<1% 41	.8%
Immediate Post Infusion			41	.8%
1 hr " 4 hr " 12 hr "				
4 hr " " 12 hr " "			38	
12 hr " "				.4%
12 m	Latita.		38	.4%
24 hr " "			31	.4%
			.11	.9%
hr " "				
ADVERSE EFFECT		and an is a state	Magni Salar	
SYMPTOMS OF SIGNS OF ONSET	DURATION		SEVERITY	•
	enis Alphile A Gi ⁿ y			
*Classify reaction as1 = mild; 2 = moderate; 3				

	Patient Identifice Age_27_(yrs) Wei	P: tion ght70 (kg) (DPHILIC FAC rotocol No. pr(<i>lbs</i> , MEDICAL HIST	101 / Height <u>5'9"</u>		168 tudy No. 2 Case No. 2
	Hypertension	XX No Yes X No Yes X No Yes	Hepatitis Jaundice HAA Test	X No X No	Yes Yes Positive	Date Date Date
6	X No	REACTIONS	an a	D <u>US</u> THERAPY? Dlease specify	i therapy and i	reaction:
6		PHYS	JICAL EXAMIN	JATION		
	<u>Number</u> and list of treatment examine Use additional m	each positive f ation, use same	<u>inding</u> in p number and	re-treatment indicate any	changes in ec	On post- ach finding.
	P.E. WNL Exc. fo	and the second	l right	P.E. unch	Post-Treatment	
0	knee deformity a		DIAGNOSIS			
	Prophylaxis	Joint ; Massiv	Hemorrhage e Wound MITANT MEDI <i>Ument or be</i> g	Surger:		2000750
*	. DRUG	SINGLE DOSE	ROUTE (IM, IV, PO)	SCHEDULE	DATE STARTEI	DATE STOPPED
4년 전문 1948년 11년	DILANTIN	100 mg	P.0.	, T.I.D.	10/1	
	ELAVIL	150 mg	P.0.	G.H.S.	10/14	
	DEMEROL	50 mg	P.0.	Q6H PRN pair	10/16	
						· Passing and

Preinfusion <1% Immediate Post Infusion <1% 1 hr " 1 hr " 4 hr " 12 hr " 24 hr " ADVERSE EFFECT	Date	Hemo	oglobin	Hematoo	rit	HAA	Biliru	bin.	S.G.O.T.	169
Lot No. <u>K852032</u> Dosege <u>2436</u> AHF units in <u>60</u> m1 AHF units/vial_ <u>1218</u> Solution Time <u>50</u> (minutes) Infusion Time <u>30</u> (minutes) Calculated AHF Rise <u>88</u> Actual AHF Rise <u>55</u> a Date Time B.P. Pulse Temp. PTT AN Preinfusion	. 10/18/3	77	.3	43.8		·NEG .	.4		39	1.143
.ot No. K852032 Dosage 2436 AHF units in 60 ml WF units/vial_1218 Solution Time 50 .(minutes) Infusion Time 30 (minutes) Calculated AHF Rise 88 * Actual AHF Rise 55 * Date Time B.P. Pulse Temp. PIT Preinfusion				· •	4	į.	8 × 3		i ge	1. A. C.
HF units/vial_1218 Solution Time 50 (minutes) Infusion Time 30 (minutes) Calculated AHF Rise 88 Actual AHF Rise 55 2 Date Time B.P. Pulse Temp. PIT Au And And And And And Preinfusion Immediate Post Infusion Immediate And And And 1 hr " Immediate And And And 24 hr " " Immediate Adverse effects B ADVERSE EFFECT Adverse effects as in table: SEVERITIN SEVERITIN				AL-12	59 ADMI	NISTRATIC	Ń.			
Calculated AHF Rise BB Actual AHF Rise 55 Temp. PIT Al Preinfusion	ot No.	K852032	Do	osage 24	36	AHF unit	s in <u>60</u>		ml	
Date Time B.P. Pulse Temp. PTT Al Preinfusion	AHF unit	s/vial_12	218 Sc	olution T	ime _50	(minut	es) Infu	sion Ti	me <u>30</u>	(minute:
Preinfusion <1%		Calcula	ited AHF	Rise	~	Actual	AHF Rise	-55	\$	
Immediate Post Infusion 55 1 hr " 4 hr " 4 hr " 1 hr " 4 hr " 4 hr " 1 hr " 2 hr " 24 hr " - hr - hr ADVERSE EFFECT ADVERSE effects Adverse effects as in table:		1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 - 1997 -		Date	Time	в.Р.	Pulse	Temp.	PIT	AHF%
Immediate Post Infusion 46 1 hr " 4 hr " 4 hr " 12 hr " 12 hr " 24 hr " - hr " ADVERSE EFFECT ADVERSE EFFECT SYMPTOMS OF STENS DATE AND TIME DIRATION SEVERITY	Preinf	usion .	1							<1%
4 hr " 37 4 hr " 37 12 hr " 28 24 hr " 28 24 hr " 9	Immedi	ate Post	Infúsion							`55%
12 hr " 28 24 hr " 9 hr " 1 ADVERSE EFFECT	1 hr	11	Π.		<u>A</u> M					46.13
24 hr " 9 _hr " 9 _hr " 9 _ hr " 10 _ ADVERSE EFFECT	4 hr	23	и							37.1%
hr " ADVERSE EFFECT ADVERSE EFFECT ADVERSE effects as in table: SYMPTOMS DE STENS DATE AND TIME DURATION SEVERITY	12 hr	77	n							28%
ADVERSE EFFECT ADVERSE EFFECT Adverse effects as in table:	24 hr		n							9.2%
No adverse effects Adverse effects as in table: SYMPTOMS OF SIGNS DATE AND TIME	hr									
	No a	adverse e	ffects	A			cts as ir	table		
	SYMPTO	MS OF SI	GNS				DURATION		SEV	/ERITY*
				、生きの朝) 認知·博 12					
*Classify reaction as1 = mild; 2 = moderate; 3 = severe	00115		1.5 A 1.4							a tha a feature
									APOnor	10 - Marcola 10 - Alberto
AP000751										

т Ц	$\left(\begin{array}{c} x & x \\ x & y \\ z \end{array} \right) = \left(\begin{array}{c} x & y \\ y \end{array} \right) \left(\begin{array}{c} x \end{array} \right) \left(\begin{array}{c} x \\ y \end{array} \right) \left(\begin{array}{c} x \end{array} \right) \left(\begin{array}{c} x \end{array} \right) \left(\begin{array}{c} x \end{array} \right) \left(\begin{array}{c} x$	ANTIHE	EMOPHILIC FAC Protocol No.			179
	Patient Identifica	tion		1	S	tudy No. 2
3	Age 30 (yrs) Weig	ght (kg)	or 211 (125) Height ^{5'8"}	(in)	Case No. 3
			MEDICAL HIS	TORÝ		y Neller
	Kidney Disease [X No Yes	Hepatitis	X No	Yes	Date
	Hypertension [X No 🗌 Yes	Jaundice	No No	Yes	Date
	Uremia [X No Yes	HAA Test	Negative	Positive	Date <u>9/16/77</u>
		REACTION	IS FROM <u>PREVIO</u>	DUS THERAPY?		
1 194 1 1 1 1 201	X No	×, q. ⊂ s _ j	🗌 Yes; p	clease specify	therapy and a	reaction:
	2	a.		de Martine I		• 500 (1) 10 - 10 - 10 - 10 - 10 - 10 - 10 - 10 -
	1			6 121936, - c	alia, ang	See Lindskie
الم زيدي	· · · ·					t della pe
÷.,		РН	YSICAL EXAMIN	VATION		
	<u>Number</u> and list e treatment examina Use additional nu	tion. use sa	me number and	l indicate any	changes in ec	On post- ach finding.
	Pre-	Treatment			Post-Treatment	
	1. Right femoral	pseudo tumor		1. no chan	ge	a, gillina,
·	Υ.	-				
್ 🔊			「新たいの構成」			
5 N 1	· · · · · · · · · · · · · · · · · · ·	1 2 ⁸	DIAGNOSIS			
	Propnylaxis	. Joint	: Hemorrhage	Muscle	Hemorrhage	
6. 24	Overt Bleeding	☐ Massi	ive Wound	X Surgery		
	i det di di di	CONC	COMITANT MEDI	and the Colorestee	A	P000752
	DRUG	SINGLE · DOSE	ROUTE (IM, IV, PO)	SCHEDULE	DATE	DATE STOPPED
		300 mg	PO	- QID	9/14/77	12/9/77
- 1913	Colace	the second se		anti a trata anti-	States a states a	
	Valium	5 mg •	PO	Øeh	9/12/77	12/9/77
	A CALLER DOLLAR - REPORTED	5 mg .	PO PO	Q6H Q4H	9/12/77	and the state of

Date	Hemoglobin	Hematoc	rit	HAA	Biliru	ubin.	S.G.O.T.	17
9/12/77		43.9		.()	.9		. 17	-156-4
11/12/77	13.1	38.3		()	1.0		17	
ot No. K8	52032 Do		1. 1.	NISTRATIC	100		ml	
	ial <u>1218</u> So alculated AHF			网络缺乏到	La Barriera La	Station in	Gusterit,	(minut
*.	11/16/77	Date	Time		``Pulse	1000		AHI
Preinfusio	in		18 13 14					<1%
Immediate	Post Infusion	1 1 1						74%
1 hr	н , , , , , , , , , , , , , , , , , , ,		· 1.例					Clot
4 hr	8 N							.57.
12 hr	н							34.
24 hr	n n	2.1						12.
hr	n ř							
X No adve		desist in a	D TIME	erse effe	cts as ir DURATION		Constants. Const	ERITY
*Classify :	reaction as1 = ponseSa	= mild; 2 tisfactor		erate; 3	= severe			
Clinical Resp	ad picture. P			가지가 가지 않다. 지지 가지 않다. 같다.		siger have		
Clinical Resp						Asirina		

		AL-1259 10PHILIC FAC	TOR (HUMAN)		172
		Protocol No.	iui .	n in the second se	
Patient Identificat				1.50	Study No2
Age 49 (yrs) Weig	t(<i>kg</i>)	or 160 (1bs) Height <u>5'11</u>	<u>"</u> (in)	Case No. <u>4</u>
R 11	5	MEDICAL HIS	TORY		
Kidney Disease [K) No 🗌 Yes	Hepatitis	□ No	X Yes	Date 1972
Hypertension [No X Yes	Jaundice	X No	Yes	Date
Uremia 🛛	No Yes	HAA Test	X Negative	Positive	Date 1/21/
	REACTIONS	FROM PREVIO	DUS THERAPY?		
X No		Yes;]	 please specify	ı therapy and	reaction:
en en el construction de la constru La construction de la construction d	a nga s				and a starting of the
	, P.M.	(
	PHY	SICAL EXAMIN	VATION ,	in North	
<u>Number</u> and list en treatment examina Use additional num	tion, use same	e number and	l indicate any	changes in e	On post- each finding.
Pre-	Treatment			Post-Treatmen	t
1. Deformity and S	welling R. Kn	ee and	1. Decreased	; swelling of R	. Knjee
L. Knee		le ristlike Miles			s di Mana
n - vaj	17 - 1898) 1			and the second	
the share with		DIAGNOSIS			
Prophylaxis	X Joint	Hemorrhage	Muscle	Hemorrhage	
Overt Bleeding	🗌 Massiv	/e Wound	Surger	у .	
٩Ľ)	CONCC 1 use at enrol	MITANT MEDI liment or be	CATIONS gun during st	udy)	
DRUG	SÎNGLE DOSE	ROUTE (IM, IV, PO)	SCHEDULE	DATE	
Hydrodiurel	50 mg	PO	BÍD	dis. definiti	
Librium	25 mg	PO	QHS	AP00075	4
		and the second			a manager
and the state of the state		and a second second	S. S. Sugar Sect.		in a starting

Date	Hemoglobin	Hematoc	rit	HAA	Biliru	ibin	S.G.O.T.	17
.11/14/77.	15.6	45.0		Neg.	.3	ί. ·	32	1. jeta
	· .	· ·					195 _{6 d} ala	n, gleddir
	852032 Do	osage 2	436	1. A.	;s in <u>60</u>	1997 1983	_ml ·	(minute
	Calculated AHF		the state of	机运输工程的			建物学 医小白的	
	11/4/77		67 T X - 1	B.P.	101 1134			AHF%
Preinfusi	ion							1.6%
Immediate	Post Infusion			道:"停 急。"				36.3%
1 hr	н л							
4 hr	P7 P3							
12 hr								
24 hr								
hr	н п							
	erse effects OF SIGNS	AL DATE AN OF OI	D TIME	EFFECT erse effe	DURATION			EVERITY*
			ulan n Ulan in					
						G. 7777 44		Sec. A State
*Classify Clinical Re	reaction a ^s 1 sponse	= mild; 2 Satisfac		erate; 3	= severe			
	날씨는 가지 않는			erate; 3	= severe -			
	날씨는 가지 않는	Satisfac	tory	erate; 3				
	날씨는 가지 않는	Satisfac ,	tory			A	P000755	

	X Prophylaxis Overt Bleedin (. DRUG None	g 🗌 Massiv	DIAGNOSIS Hemorrhage Ye Wound DMITANT MEDI Tament or bea ROUTE (IM, IV, PO)	Surger	idy)	
	Overt Bleedin (. DRUG	g Massiv CONCC In use at enrol	Hemorrhage We Wound MITANT MEDI Unent or be ROUTE (IM, IV, PO)	CATIONS gun during sta	ر برگیر) DATE	
	Overt Bleedin	g Massiv CONCC In use at enrol	Hemorrhage We Wound MITANT MEDI Coment or beg ROUTE (IM, IV,	CATIONS Gun during sta	ر برگیر) DATE	
	Overt Bleedin	g 🗌 Massiv CONCC	Hemorrhage Ve Wound MITANT MEDI	Surger	/: 	
	<u> </u>	1 (1994) (1994) (Hemorrhage			
	X Prophylaxis		• 18 17 18 Mar	Muscle	Hemorrhage	
						1. 1. 1997
	•		"动动"的分			27 (MARCA)
-	L. Elbow, R. Kr	nee and R. Shou	lder			da i georgial Referencia
11	. Chronic deform	ity and limited	R.O.M. of	1. No change		
	Pre	-Treatment		an a	Post-Treatmer	it
	<u>Mumber</u> and list treatment examin Use additional m	ation, use same	e number and	indicate any	changes in e	On post- each finding
_		والمتحد المحكورة والمحاد	SICAL EXAMIN			
-				dertette, eik	rial Alla	
-						
÷		All Andrews	entres. L'anticipation			
	X No		🗌 Yes; p	lease specify	therapy and	reaction:
-	54 5	REACTIONS	FROM PREVIC	US THERAPY?		:
	Uremia	X No Yes	HAA Test	X Negative	Positive	Date <u>11/4</u>
	Hypertension	X No: Yes	Jaundice	No No	Yes	Date
	Kidney Disease	X No Yes	Hepatitis	X No	Yes	Date
	Le.		MEDICAL HIS	ORY	的。他们	
	ge(yrs) We	ight(kg)	or 115 (2bs.	Height 5'5"	(in)	Case No.
A	. 32					
•	atient Identific	ation				Study No. 2

	Hemo	globin	Hematoc	rit	HAA	Biliru	Jbin	S.G.O.T.	11
11/7	7	400 K.A.			·()				1.5.5
		•				1.00			in der
-	K852032		sage	218	an Ar	ts in <u>3</u>	ada -	T MAD	(minus
						AHF Rise			
			Date	A 68'		THE CONTRACT.	181.1	- • PTT	AH
Preinfu	usion				学学				<1%
Immedia	ate Post :	Infusion							26
1 hr	H					なる	協力		
4 hr	п	"							多德
12 hr	"						振行		
24 hr	п	n							》 得
The second s	and a set of the set of the set of the set	and the second sec			and and the second s				
hr	7	1 3.47							
X No a	" dverse ef	fects	DATE AN	e e l'antigation de la construcción de la construcción de la construcción de la construcción de la construcción La construcción de la construcción d	ながも必	DURATION			
SYMPTO	dverse ef MS OF SIG fy reacti	fects	DATE AN	Adve D TIME VSET	erse effe	DURATIO			VERITY
X No a SYMPTO	dverse ef MS OF SIG fy reacti	fects	DATE AN OF ON	Adve D TIME VSET	erse effe	DURATIO		SE	VERITY

Patient Identif	ication		-14 		Study No.
Age24 (yrs)	Weight(k	g) or 115 (200	s) Height	(in) ·	Case No.
in contract in contract.	Ę.	MEDICAL HIS	STORY		. 3
Kidney Diseas	e X No	Yes Hepatitis	x No	Yes	Date
Hypertension	X No	Yes Jaundice	X No	Yes	Date
Uremia	X No	Yes HAA Test	X Negative	Positive	Date 8/1
	REACT	IONS FROM PREVI	OUS THERAPY?		
X No		- 0 Real	please specify	therapy and	reaction:
		- Sel Friday			
				To Addition of	
		······································		的人的社会们	
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treatment exam	st each positi mination, use	PHYSICAL EXAMI ve finding in ; same number an	pre-treatment d indicate any	changes in a	On post- each findi
treatment exam Use additional	st each positi mination, use	ve finding in j	pre-treatment d indicate any sitive finding	changes in a	each findin
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treatment exam Use additional	st each positi mination, use l numbers to l Pre-Treatment	ve finding in ; same number an ist any new po	pre-treatment d indicate any sitive finding	c <u>hanges</u> in e s. Post-Treatmen	each findir
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<pre>*Classify reaction as 1 = mild; 2 = moderate; 3 = severe Clinical Response</pre>			ا بەرىلار ئا	el pada	fla I		1			
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<u>.</u>		MOPHILIC FAC Protocol No.			17
Patient Identifica	ation			n a stale The second a	Study No.
Age_30 (yrs) Wet	ight(kg)	or 135 (2bs.	Height 5'8"	(in)	Case No.
	- R	MEDICAL HIST	fory .		
Kidney Disease	X No Yes	Hepatitis	No No	Yes	Date
Hypertension	X No Yes	Jaundice	□ No	Yes	Date
Uremia	X No Yes	HAA Test	X Negative	Positive	Date <u>9/23</u>
	REACTION	S FROM PREVIC	US THERAPY?		
No		X Yes; p	lease specify	therapy and	reaction:
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		AL-1259 MOPHILIC FACT Protocol No.			180
Patient Identificat		•		St	udy No. 2
Age 8 <i>(yrs)</i> Weig		or 75 (1bs)	Height 4'3"		Case No. 8
		MEDICAL HIST	ORY .		
Kidney Disease [X No Yes	Hepatitis	X No	Yes	Date
Hypertension [X No Yes	Jaundice	X No	Yes	Date
Uremia [X No 🗌 Yes	HAA Test	X Negative	Positive	Date
· · · ·	REACTIONS	FROM PREVIC	US THERAPY?		
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1.5. STUDY 3 - Evaluation of AL-1259 by Dr. M. W. Hilgartner

Dr. Hilgartner studied 3 paediatric and 2 adult patients with the established diagnosis of Haemophilia A. One paediatric patient was treated on two occasions of joint haemorrhage, one paediatric patient on one occasion of joint haemorrhage, and the third paediatric patient received prophylactic treatment. One adult patient was prepared for surgery and the other received prophylactic treatment. On the first treatment of patient MC, the in-vivo recovery of AHF activity was poor. It is possible that an undetected low titre inhibitor of AHF may have been present; this has been reported in as many as 20% of haemophilic patients. Leaving this one treatment out of consideration, recovery of AHF in-vivo in the five patients averaged 83% of the expected values. No adverse effects were observed. The results of this study are tabulated overleaf.

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		11/23/77	7 Date	Time	в.Р.	Pulse	Temp	D. PTT	AHF
Pre	einfusio	on	11/23						4.8%
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		sponse Sa	tisfactory	<u>.</u>				АР	000763

STUDY 3 - MARGARET W. HILGARTNER, M.D.

TABULATED RESULTS

Patient	Age	Wt. Kg.	Treatment	Dose* Units	Calculated Rise % AHF	Observed Rise % AHF	Adverse Effects
	27	90.5	Surgery Preparation	2436	54	44	None
	15	46.4	Joint Haemorrhage	. 2436	105	88	None
	25	85.5	Prophylactic	2436	57	31	None
	7	24.5	Joint Haemorrhage 11-4	2436	191**	94**	None
- -	12.12	24.5	Joint Haemorrhage 12-15	1218	96	98 .	None
	17	70.5	Prophylactic	1218	35	33	None

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AP000765

*AL-1259 Lot K852032, 1218 AHF units per vial **Value not included in average. See explanation, report of evaluation, Study 3

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Patient Identifica	ation				Study No.
Age_27_(yrs) We:	ight <u>90.5</u> (kg)	or(lbs,	Height701	(in)	Case No.
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Kidney Disease	No X Yes	Hepatitis	X No	Yes	Date
Hypertension	X No Yes	a second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second second s	X No	Yes	Date
Uremia	X No Yes	HB Ag HAA Test	X Negative	HB AG Pos	e Date
	REACTIONS	S FROM PREVIC	US THERAPY?		
No No		X Yes; p	lease specify	therapy and	l reaction:
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Hypertension	No Yes	Jaundice	🕅 No	Yes	Date
Uremia	No Yes	HAA Test	📉 Negative	Positive	Date
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AL-1259 ADMINISTRATION .ot No. 1259 Dosage 2436 AFF units in 60 m1 .hff units/viel_1218 Solution Time (minutes) Infusion Time (minutes) Caloulated AFF Rise 191_3 Actual AFF Rise 94_3 2 Date Time B.P. Pulse Temp. PT AFF3 Preinfusion 11/4/27 B0 Less than i hr 11/4/27 B0 Less than i hr 11/4/77 B0 Less than i hr 11/4/77 B0 Less than i hr 11/4/77 B0 Less than i hr No adverse effects 11/4/77 B4 i hr Abverse effects as in table: Abverse effects as in table: SYMPTOMS DF SIGNS DATE AND TIME DURATION SEVERITY* *Classify reaction as 1 = mild; 2 = moderate; 3 = severe Einicel Response Severe	11/4/77	12.1	33.5	····· .	Neg.	0.	4	180	ang Breathrach
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Hypertension [X No Yes	Jaundice	X No .	Yes	Date
Uremia (X No 🗌 Yes	HAA Test	X Negative	🗌 Positiv	e Date
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4 hr "		13-6					
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Patient Identifica	ation				Study No.
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		MEDICAL HIS	e l'interface		r Tring Tring
Kidney Disease	X No Yes	Hepatitis	X No	Yes	Date
Hypertension	X No Yes	Jaundice	X No	Yes	Date
Uremia	X No Yes	HAA Test	X Negative	🗌 Positive	Date
	REACTIONS	S FROM PREVIO	DUS THERAPY?		
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1.6. STUDY 4 - Evaluation of AL-1259 by Dr. P. H. Levine

Dr. Levine studied one paediatric and four adult patients with established diagnosis of Haemophilia A. Two patients were treated for joint haemorrhage and one received prophylactic treatment. One patient was prepared for arthroscopy and one received pre and post-operative treatment in a total hip replacement. The clinical response in the latter case was deemed unusually good in that this major operation was uneventful and there was no post-operative bleeding. No adverse effects were observed in any of the five patients. Recovery of AHF activity <u>in-vivo</u> averaged 116% of the calculated value. The clinical response was satisfactory in each case. The results of this study are tabulated overleaf.

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Patient	Age	Wt. Kg.	Treatment	Dose* Units	Calculated Rise % AHF	Observed Rise % AHF	Adverse Effects
	28	70	Surgery Preparation	3942	100	117	None
	38	85	Surgery Preparation Post Operative	2628 1314	66 32	72 42	None None
	13	30	Joint Haemorrhage	1314	88	86	None
- - 1	24	54	Joint Haemorrhage	1314	48	55	None
	33	71	Prophylactic	1314	38	49	None

STUDY 4 - PETER H. LEVINE, M.D. TABULATED RESULTS

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*AL-1259 Lot K852030, 1314 AHF units per vial

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197.

	Patient Identifica			101 .		198 Study No. <u>4</u>
,	Age <u>28 (yrs)</u> Wei	ght <u>70</u> (<i>kg</i>)	or(lbs) MEDICAL HIST	Section Section	(in)	Case No. <u>1</u>
	Kidney Disease	X No Yes	Hepatitis	No No	Yes .	Date
	Hypertension	X No Yes	Jaundice	No No	Yes .	Date
	Uremia	🗙 No 🗌 Yes	HAA Test	Negative	Positive	Date
* .* .*	No	REACTION	S FROM <u>PREVIC</u> Yes; p	D <u>US</u> THERAPY? lease specify	therapy and	reaction:
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		PHY	SICAL EXAMIN	ATION		
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•	1 hr		11/2	2.00 PM	120/80	60	98.6	47.8	56
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Dvert Bleeding (In DRUG	CONCO use at enrol SINGLE DOSE	MITANT MEDI Iment or be ROUTE (IM, IV, PO)	CATIONS gun during sta	DAT	TED STOP

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209 . Hemoglobin Hematocrit HAA Date Bilirubin S.G.O.T. 1/26/78 41 ... Neg. 0.8 60 . . AL-1259 ADMINISTRATION Lot No. ______K852030 Dosage 1314 AHF units in 30 ml AHF units/vial_1314 Solution Time 20 (minutes) Infusion Time 8 (minutes) ... Calculated AHF Rise 38 % Actual AHF Rise 49 % B.P. Pulse Temp. PTT Date Time AHF% 1/27/78 8:00 140/80 Preinfusion .80 98.8 55 9 AM **i** 1/27/78 8:10 144/80 Immediate Post Infusion 84 98.6 45 58 AM . n 10 1 hr 1/27 9:05 136/82 80 98.6 44 52 AM. и n . 4 hr 1/27 noon 140/80 80 98.5 45 33 ... 17 77 12 hr 1/27 2:00 144/84 85 98.8 47 26 PM 27 ** 24 hr 1/28 8:00 140/84 76 98.8 54 ... 8.5 AM 'n 11 hr 10 ADVERSE EFFECT Adverse effects as in table; X No adverse effects DATE AND TIME SYMPTOMS OF SIGNS DURATION SEVERITY* OF ONSET *Classify reaction as1 = mild; 2 = moderate; 3 = severe · No hemorrhage , Clinical Response See . 2 2017年1月 · 资料 AP000791 Date 1/31/78 , M.D. Cimphung - 0